

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALVOTECH USA INC. and ALVOTECH HF,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case: PGR2025-00085
U.S. Patent No. 12,168,036

PATENT OWNER'S RESPONSE

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TABLE OF AUTHORITIES

CASES

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<i>Allergan v. MSN</i> , 111 F.4th 1358 (Fed. Cir. 2024)	64, 65, 79, 83
<i>Allergan v. Sandoz</i> , 796 F.3d 1293 (Fed. Cir. 2015)	passim
<i>Apple v. Samsung</i> , 839 F.3d 1034 (Fed. Cir. 2016) (en banc)	19
<i>Arbutus Biopharma v. ModernaTX</i> , 65 F.4th 656 (Fed. Cir. 2023)	65, 80
<i>Arctic Cat v. Bombardier Recreational Prods.</i> , 876 F.3d 1350 (Fed. Cir. 2017)	18
<i>Blackberry v. Zipit Wireless</i> , IPR2014-01509, 2016 WL 1244943 (P.T.A.B. Mar. 29, 2016).....	64, 68
<i>BMW v. Stragent</i> , IPR2017-00676, 2018 WL 3005913 (P.T.A.B. June 14, 2018).....	66
<i>California v. Green</i> , 399 U.S. 149 (1970).....	1
<i>Chemours Co. FC, LLC v. Daikin Indus.</i> , 4 F.4th 1370 (Fed. Cir. 2021)	58
<i>Cooper Cameron v. Kvaerner Oilfield Prods.</i> , 291 F.3d 1317 (Fed. Cir. 2002)	76
<i>Cordis v. Medtronic</i> , 339 F.3d 1352 (Fed. Cir. 2003)	77

<i>DePuy Spine v. Medtronic</i> , 567 F.3d 1314 (Fed. Cir. 2009)	18, 32, 41
<i>E.I. DuPont v. Synvina</i> , 904 F.3d 996 (Fed. Cir. 2018)	57
<i>Endo Pharm v. Actavis</i> , 922 F.3d 1365 (Fed. Cir. 2019)	44, 50
<i>Genetics Inst. v. Novartis</i> , 655 F.3d 1291 (Fed. Cir. 2011)	23
<i>Gentry Gallery v. Berkline</i> , 134 F.3d 1473 (Fed. Cir. 1998)	76
<i>Harari v. Lee</i> , 656 F.3d 1331 (Fed. Cir. 2011)	65, 80
<i>Hayward Indus. v. Pentair Water Pool & Spa</i> , 721 F. App'x 974 (Fed. Cir. 2018)	65
<i>Honeywell v. Mexichem Amanco Holding</i> , 865 F.3d 1348 (Fed. Cir. 2017)	44
<i>In re Applied Materials</i> , 692 F.3d 1289 (Fed. Cir. 2012), and (2)	20, 62
<i>In re Cyclobenzaprine Pat. Litig.</i> , 676 F.3d 1063 (Fed. Cir. 2012)	18
<i>In re Entresto</i> , 125 F.4th 1090 (Fed. Cir. 2025)	76, 77
<i>Intuitive Surgical v. Ethicon</i> , IPR2018-01248, 2020 WL 594140 (P.T.A.B. Feb. 6, 2020)	64, 68
<i>Janssen Pharm. v. Teva</i> , 141 F.4th 1367 (Fed. Cir. 2025)	20, 40, 46, 50
<i>KSR Int'l v. Teleflex</i> , 550 U.S. 398 (2007)	18
<i>LizardTech v. Earth Resource Mapping</i> , 424 F.3d 1336 (Fed. Cir. 2005)	84

<i>McRO v. Bandai Namco Games</i> , 959 F.3d 1091 (Fed. Cir. 2020)	64, 85
<i>Meiresonne v. Google</i> , 849 F.3d 1379 (Fed. Cir. 2017)	19
<i>Millennium Pharms. v. Sandoz</i> , 862 F.3d 1356 (Fed. Cir. 2017)	19, 54, 55
<i>ModernaTx v. Arbutus Biopharma</i> , 18 F.4th 1364 (Fed. Cir. 2021)	19, 41
<i>Ortho-McNeil Pharm. v. Mylan Labs.</i> , 520 F.3d 1358 (Fed. Cir. 2008)	18
<i>Otsuka Pharm. v. Sandoz</i> , 678 F.3d 1280 (Fed. Cir. 2012)	18
<i>Paice v. Ford Motor</i> , 881 F.3d 894 (Fed. Cir. 2018)	65, 80
<i>Pernix Ireland Pain DAC v. Alvogen Malta Operations</i> , 323 F. Supp. 3d 566 (D. Del. 2018).....	74
<i>Pfizer Inc. v. Teva Pharm. USA, Inc.</i> , 460 F. Supp. 2d 659 (D.N.J. 2006).....	54
<i>Pfizer v. Apotex</i> , 480 F.3d 1348 (Fed. Cir. 2007)	44, 47, 50
<i>Polaris Indus. v. Arctic Cat</i> , 882 F.3d 1056 (Fed. Cir. 2018)	18, 19, 53
<i>Regeneron Pharm., Inc. v. Mylan Pharm. Inc.</i> , 127 F.4th 896 (Fed. Cir. 2025)	passim
<i>Regeneron Pharm., Inc. v. Mylan Pharm. Inc.</i> , 714 F. Supp. 3d 652 (N.D.W.Va. 2024).....	2
<i>UCB v. Actavis Labs.</i> , 65 F.4th 679 (Fed. Cir. 2023)	19, 62

<i>Zoltek Corp. v. US</i> , 815 F.3d 1302 (Fed. Cir. 2016)	64
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OTHER AUTHORITIES

37 C.F.R. §42.204(b)(4).....	60
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LIST OF EXHIBITS

Exhibit	Description	Filed
2001	Excerpts from the File History of U.S. Appl. No. 17/384,070	X
2002	US 2018/0326126 (“Fiedler ’126”)	X
2003	Australian Dep’t of Health & Human Aging, Australian Public Assessment Report for Aflibercept (July 2012) (“AusPAR”)	X
2004	Ameya U. Borwankar et al., <i>Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine.HCl and Arginine.Glutamate</i> , 55 Ind. Eng. Chem. Rsch. 11225 (2016) (“Borwankar”)	X
2005	Neal Whitaker et al., <i>A Formulation Development Approach to Identify and Select Stable Ultra-High-Concentration Monoclonal Antibody Formulations with Reduced Viscosities</i> , 106 J. Pharmaceutical Scis. 3230 (2017) (“Whitaker”)	X
2006	Ameya U. Borwankar et al., <i>Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine.HCl and Arginine.Glutamate: Supplementary Information</i> , 55 Ind. Eng. Chem. Rsch. 11225 (2016) (“Borwankar SI”)	X
2007	Eylea HD® Highlights of Prescribing Information (Oct. 2024)	X
2008	AbbVie, Allergan, an AbbVie Company, and Molecular Partners Receive Complete Response Letter from FDA on Biologics License Application for Abicipar Pegol, AbbVie News Center (June 26, 2020), https://news.abbvie.com/2020-06-26-Allergan-an-AbbVie-Company-and-Molecular-Partners-Receive-Complete-Response-Letter-from-FDA-on-Biologics-License-Application-for-Abicipar-pegol (“AbbVie Press Release”)	X

Exhibit	Description	Filed
2009	Rod McNeil, <i>Advances and Developments in Medical Retina</i> , 25 Eye News 1 (2019) (“McNeil”)	X
2010	Rehan M. Hussain & Thomas A. Ciulla, <i>Emerging Vascular Endothelial Growth Factor Antagonists to Treat Neovascular Age-Related Macular Degeneration</i> , 22 Expert Op. Emerging Drugs 235 (2017) (“Hussain”)	X
2011	Angus Liu, <i>Novartis Calls off 3 Beovu Trials Testing More Frequent Dosing on Concerns of Vision-Threatening Side Effect</i> , FiercePharma (June 1, 2021) (“Liu 2021”)	X
2012	Beovu Label (2024)	X
2013	Philip J. Rosenfeld & David J. Browning, <i>Editorial: Is This a 737 Max Moment for Brolicizumab?</i> , 216 Am. J. Ophthalmology A7 (2020) (“Rosenfeld”)	X
2014	J. Gaudreault et al., <i>Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) After a Single Intravitreal Administration</i> , 46 Invest. Ophthalmol Vis. Sci. 726 (2005) (“Gaudreault”)	X
2015	Public Trial Transcript Excerpts, <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.</i> , No. 22-cv-61 (N.D.W. Va.)	X
2016	Wang, <i>Protein Aggregation and Its Inhibition in Biopharmaceutics</i> , 289 Int. J. Pharm. 1 (2005) (“Wang 2005”)	X
2017	Wang, <i>Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals</i> , 1856 Int. J. Pharm. 129 (1999) (“Wang 1999”)	X

Exhibit	Description	Filed
2018	Philip J. Rosenfeld et al., <i>Maximum Tolerated Dose of a Humanized Anti-Vascular Endothelial Growth Factor Antibody Fragment for Treating Neovascular Age-Related Macular Degeneration</i> , 112 Ophthalmology 1048 (2005) (“Rosenfeld 2005”)	X
2019	U.S. Patent Application Publication No. 2004/0197324 (“Liu 2004”)	X
2020	U.S. Patent No. 7,087,411 (“Daly”)	X
2021	WO 2006/138181 (“Gokarn”)	X
2022	Rahul N. Khurana et al., <i>Two-Year Results of the Phase 3 Randomized Controlled Study of Abicipar in Neovascular Age-Related Macular Degeneration</i> , 128 Ophthalmology 1027 (2021) (“Khurana 2021”)	X
2023	James A. Dixon et al., <i>VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration</i> , 18 Expert Opinion Investigational Drugs 1573 (2009) (“Dixon 2009”)	X
2024	Pravin U. Dugel et al., <i>HAWK and HARRIER: Ninety-Six-Week Outcomes from the Phase 3 Trials of Brodalumab for Neovascular Age-Related Macular Degeneration</i> , 128 Ophthalmology 89 (2021) (“Dugel”)	X
2025	John S.Y. Park & David R. Chow, <i>Clinical Primer on Eylea HD: Review of the Current Data</i> , Retina Specialist (Apr. 13, 2024), https://www.retina-specialist.com/article/clinical-primer-on-eylea-hd-review-of-the-current-data (“Park”)	X
2026	Vabysmo Label 2024 (“Vabysmo Label”)	X

Exhibit	Description	Filed
2027	Jonas L. Fast et al., <i>Physical Instability of a Therapeutic Fc Fusion Protein: Domain Contributions to Conformational and Colloidal Stability</i> , 48 <i>Biochemistry</i> 11724 (2009) (“Fast”)	X
2028	Zaltrap Label 2023 (“Zaltrap Label”)	X
2029	Michael Thomas, <i>Comparative Effectiveness of Aflibercept for the Treatment of Patients with Neovascular Age-related Macular Degeneration</i> , 7 <i>Clinical Ophthalmology</i> 495 (2013) (“Thomas”)	X
2030	Alvotech, Report of Foreign Private Issuer (Form 6-K) (June 23, 2025) (“Alvotech Press Release”)	X
2031	Molecular Partners, Molecular Partners to Regain Global Rights to Abicipar, Molecular Partners News Release Details (Aug. 8, 2021) https://investors.molecularpartners.com/news-releases/news-release-details/molecular-partners-regain-global-rights-abicipar (“Molecular Partners Press Release”)	X
2032	Novartis, <i>Novartis Reports One Year Results of Phase III MERLIN Study Evaluating Beovu® Every Four Week Dosing and Provides Update on Beovu Clinical Program</i> , Novartis Media Releases (May 28, 2021) https://www.novartis.com/news/media-releases/novartis-reports-one-year-results-phase-iii-merlin-study-evaluating-beovu-every-four-week-dosing-and-provides-update-beovu-clinical-program (“Novartis Press Release”)	X
2033	U.S. Patent Application Publication No. 2023/0416353	X
2034	WO 2014/009465	X
2035	U.S. Food & Drug Admin., Eylea HD Approval Letter (Aug. 18, 2018) (“Eylea HD FDA Approval Letter”)	X

Exhibit	Description	Filed
2036	Gerard A. Rodrigues, <i>Functional Characterization of Abicipar-Pegol, an Anti-VEGF DARPIn Therapeutic That Potently Inhibits Angiogenesis and Vascular Permeability</i> , 59 <i>Investigative Ophthalmology & Visual Science</i> 5836 (2018) (“Rodrigues 2018”)	X
2037	Declaration of K. Kayali	X
2038	Petition for Post Grant Review of United States Patent No. 12,158,036, Paper No. 2, PGR2025-00085	X
2039	Robert J. Falconer, <i>Advances in Liquid Formulations of Parenteral Therapeutic Proteins</i> , 37 <i>Biotechnology Advances</i> 1 (2019) (“Falconer 2019”)	X
2040	18th Annual Conference, Bioprocessing Network 2025, Conference Schedule (“Conference Schedule”)	X
2041	D’Amico article, <i>American Journal of Ophthalmology</i> , August, 1985	X
2042	Talamo article, <i>American Journal of Ophthalmology</i> , December, 1985	X
2043	Oum article, <i>Graefe’s Archive for Clinical and Experimental Ophthalmology</i> 1992	X
2044	Sakarya article, <i>European Journal Ophthalmology</i> 2010	X
2045	Macugen Highlights of Prescribing Information, Bates ALVOTECH 1048	X
2046	Deposition Transcript of Dr. Robert J. Falconer (May 27, 2026)	X
2047	U.S. Patent No. 7,396,664	X

Exhibit	Description	Filed
2048	U.S. Patent No. 7,354,579	X
2049	H. Abe, <i>Role of Histidine-Related Compounds as Intracellular Proton Buffering Constituents in Vertebrate Muscle</i> , 65 Biochemistry (Moscow) 757 (2000)	X
2050	U.S. Patent App. Pub. 2011/0027292	X
2051	Declaration of Bernhardt Trout (June 19, 2026)	X
2052	Declaration of Neil Bressler (June 19, 2026)	X
2053	Deposition Transcript of Dr. Donald J. D'Amico (June 2, 2026)	X
2054	Excerpts from File History of U.S. Patent Application No. 16/409,631	X
2055	Excerpts from the Oxford Dictionary of Biochemistry and Molecular Biology (2d ed. 2000)	X
2056	Francis A. Carey & Robert M. Giuliano, Organic Chemistry, Chapter 25 (8th ed. 2011)	X
2057	Excerpts from the Handbook of Pharmaceutical Excipients (4th ed. 2003) (“HPE”)	X
2058	Aruffo, <i>Immunoglobulin Fusion Proteins</i> , in Antibody Fusion Proteins 221 (Chamow & Ashkenazi eds., 1999) (“Aruffo 1999”)	X
2059	Avastin® Prescribing Information (2004) (“Avastin PI”)	X
2060	Bogard et al., <i>Practical Considerations in the Production, Purification, and Formulation of Monoclonal Antibodies for Immunoscintigraphy and Immunotherapy</i> , 19 Seminars in Nuclear Med. 202 (1989) (“Bogard 1989”)	X

Exhibit	Description	Filed
2061	Chang et al., <i>Practical Approaches to Protein Formulation Development</i> , in Rational Design of Stable Protein Formulations (J.F. Carpenter & M.C. Manning eds., 2002) (“Chang 2002”)	X
2062	Chi et al., <i>Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation</i> , 20 Pharm. Res. 1325 (2003) (“Chi 2003”)	X
2063	S. Duvvuri et al., <i>Drug Delivery to the Retina: Challenges and Opportunities</i> , 3 Expert Op. Biological Therapy 45 (2003) (“Duvvuri 2003”)	X
2064	Eylea® Prescribing Information (2011) (“Eylea PI 2011”)	X
2065	D. Ghate & H.F. Edelhauser, <i>Ocular Drug Delivery</i> , 3 Expert Op. Biological Therapy 275 (2006) (“Ghate 2006”)	X
2066	Lucentis® Prescribing Information (2006) (“Lucentis PI 2006”)	X
2067	Macugen® Prescribing Information (2004) (“Macugen PI 2004”)	X
2068	R.P.A. Manzano et al., <i>Testing Intravitreal Toxicity of Bevacizumab (Avastin)</i> , 26 Retina 257 (2006) (“Manzano 2006”)	X
2069	Moroney et al., <i>Aflibercept in Epithelial Ovarian Carcinoma</i> , 5 Future Oncol. 591 (2009) (“Moroney 2009”)	X
2070	M. Nagpal et al., <i>A Comparative Debate on the Various Anti-Vascular Endothelial Growth Factor Drugs</i> , 55 Indian J. Ophthalmology 437 (2007) (“Nagpal”)	X
2071	Int’l Patent Publication No. WO2005/102303 (2005) (“Peyman”)	X

Exhibit	Description	Filed
2072	Shukla et al., <i>Downstream Processing of Fc-Fusion Proteins</i> , in <i>Therapeutic Fc-Fusion Proteins</i> 97 (Chamow et al. eds., 2014) (“Shukla 2014”)	X
2073	Souillac, <i>Biophysical Characterization of Insoluble Aggregates of a Multi-Domain Protein: An Insight into the Role of the Various Domains</i> , 94 J. Pharm. Sci. 2066 (2005) (“Souillac 2005”)	X
2074	C.A. Stein & D. Castanotto, <i>FDA-Approved Oligonucleotide Therapies in 2017</i> , 25 Molecular Therapy 1069 (2017) (“Stein”)	X
2075	Wang et al., <i>Antibody Structure, Instability, and Formulation</i> , 96 J. Pharm. Sci. 1 (2007) (“Wang 2007”)	X
2076	Winter & Milstein, <i>Man-made Antibodies</i> , 349 Nature 293 (1991) (“Winter 1991”)	X
2077	Wurm et al., <i>Optimizing Production and Recovery of Immunoadhesins</i> , in <i>Antibody Fusion Proteins</i> 281 (Chamow & Ashkenazi eds., 1999) (“Wurm 1999”)	X
2078	Liu et al., <i>Reversible Self-Association Increases the Viscosity of a Concentrated Monoclonal Antibody in Aqueous Solution</i> , 94 J. Pharm. Sci. 1928 (2005) (“Liu 2005”)	X
2079	Shire et al., <i>Challenges in the Development of High Protein Concentration Formulations</i> , 93 J. Pharm. Sci. 1390 (2004) (“Shire 2004”)	X
2080	Neeraj J. Agrawal et al., <i>Computational Tool for the Early Screening of Monoclonal Antibodies for Their Viscosities</i> , 8 mAbs 43 (2016) (“Agrawal”)	X
2081	Merriam-Webster’s Medical Desk Dictionary (2002) (“Merriam-Webster”)	X

Exhibit	Description	Filed
2082	Halvor N. Christensen, <i>Proteins as Buffers</i> , Ann. 133 N.Y. Acad. Sci. 34 (1966) (“Christensen”)	X
2083	Y. Nozaki & C. Tanford, <i>Examination of Titration Behavior</i> , 11 Methods in Enzymology 715 (1967) (“Nozaki”)	X
2084	J. Wyman, <i>An Analysis of the Titration Data of Oxyhemoglobin of the Horse by a Thermal Method</i> , 127 J. Biol. Chem. 1 (1939) (“Wyman”)	X
2085	Andrew A. Moshfeghi, <i>Safety of Intravitreal Anti-VEGF Agents</i> , Review of Ophthalmology (Nov. 11, 2014), https://www.reviewofophthalmology.com/article/safety-of-intravitreal-antivegf-agents	X
2086	Joseph J. Tseng et al., <i>Sustained Increased Intraocular Pressure Related to Intravitreal Antivascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration</i> , 21 J. Glaucoma 241 (2012)	X
2087	Judy E. Kim et al., <i>Short-Term Intraocular Pressure Changes Immediately After Intravitreal Injections of Anti-Vascular Endothelial Growth Factor Agents</i> , 146 Am. J. Ophthalmol. 930 (2008).	X
2088	Evangelos S. Gragoudas et al., <i>Pegaptanib for Neovascular Age-Related Macular Degeneration</i> , 351 New Eng. J. Med. 2805 (2004)	X
2089	David M. Brown et al., <i>Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-Related Macular Degeneration</i> , 118 Ophthalmology 1089 (2011)	X
2090	Jeffrey S. Heier et al., <i>Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration</i> , 119 Ophthalmology 2537 (2012)	X

Exhibit	Description	Filed
2091	Christophe Le Tourneau et al., <i>Dose Escalation Methods in Phase I Cancer Clinical Trials</i> , 101 J. Nat'l Cancer Inst. 708 (2009)	X
2092	Jeffrey R. Sachs et al., <i>Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example</i> , 22 Clinical Cancer Rsch. 1318 (2016)	X
2093	RESERVED	
2094	Jiunn H. Lin, <i>Species Similarities and Differences in Pharmacokinetics</i> , 23 Drug Metabolism & Disposition 1008 (1995)	X
2095	Frank G. Holz et al., <i>Efficacy and Safety of Lampalizumab for Geographic Atrophy Due to Age-Related Macular Degeneration: Chroma and Spectri Phase 3 Randomized Clinical Trials</i> , 136 JAMA Ophthalmol. 666 (2018)	X
2096	Neil M. Bressler et al., <i>Intraocular Pressure Outcomes After Lampalizumab Injections in Patients with Geographic Atrophy</i> , 142 JAMA Ophthalmol. 772 (2024)	X
2097	LabChem Inc., Material Safety Data Sheet: Congo Red (CAS No. 573-58-0)	X
2098	Agar Scientific Ltd., Safety Data Sheet: Congo Red (C.I. 22120)	X
2099	Santa Cruz Biotechnology, Safety Data Sheet: Amaranth (SC-214532)	X
2100	Eduardo B. Rodrigues et al., <i>Preclinical Investigation of the Retinal Biocompatibility of Six Novel Vital Dyes for Chromovitrectomy</i> , 29 Retina 497 (2009)	X

Exhibit	Description	Filed
2101	Carolina Biological Supply Co., Safety Data Sheet: Crystal Violet (CAS No. 548-62-9)	X
2102	Ellen Kurek, <i>Conflicting Evidence over Stroke Risk from AMD Drug</i> , Pharmacy Times, available at https://www.pharmacytimes.com/view/conflicting-evidence-over-stroke-risk-from-amd-drug (last visited June 12, 2026)	X
2103	Rajendra S. Apte et al., <i>Pegaptanib 1-Year Systemic Safety Results from a Safety-Pharmacokinetic Trial in Patients with Neovascular Age-Related Macular Degeneration</i> , 114 Ophthalmology 1702 (2007)	X
2104	Bevacizumab (Avastin®) Label 2017 (Avastin Label)	X
2105	James A. Hanley & Abby Lippman-Hand, <i>If Nothing Goes Wrong, Is Everything All Right? Interpreting Zero Numerators</i> , 249 JAMA 1743 (1983)	X
2106	Mehdi Modarreszadeh et al., <i>Two Different Doses of Intravitreal Bevacizumab for Treatment of Choroidal Neovascularization Associated with Age-Related Macular Degeneration</i> , 3 J. Ophthalmic & Vision Res. 102 (2008)	X
2107	Deepika Malik et al., <i>Safety Profiles of Anti-VEGF Drugs: Bevacizumab, Ranibizumab, Aflibercept and Ziv-Aflibercept on Human Retinal Pigment Epithelium Cells in Culture</i> , 98 Brit. J. Ophthalmol. i11 (2014)	X
2108	Robert L. Avery et al., <i>Systemic Pharmacokinetics and Pharmacodynamics of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab</i> , 37 Retina 1847 (2017)	X
2109	U.S. Food & Drug Admin., <i>Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers</i> (July 2005)	X

Exhibit	Description	Filed
2110	Brandon G. Busbee et al., <i>Twelve-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration</i> , 120 Ophthalmology 1046 (2013)	X
2111	U.S. Food & Drug Admin., <i>Postmarketing Adverse Event Reporting Compliance Program</i> , https://www.fda.gov/drugs/surveillance-post-drug-approval-activities/postmarketing-adverse-event-reporting-compliance-program (last visited June 16, 2026)	X
2112	U.S. Food & Drug Admin., <i>Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients</i> (May 2005)	X
2113	Sophie Postel-Vinay et al., <i>Towards New Methods for the Determination of Dose Limiting Toxicities and the Assessment of the Recommended Dose for Further Studies of Molecularly Targeted Agents—Dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted Therapies</i> , an European Organisation for Research and Treatment of Cancer-Led Study, 50 Eur. J. Cancer 2040 (2014)	X
2114	RESERVED	
2115	V. Burckbuchler et al., <i>Rheological and Syringeability Properties of Highly Concentrated Human Polyclonal Immunoglobulin Solutions</i> , 76 Eur. J. Pharmaceutics & Biopharmaceutics 351 (2010)	X
2116	Francesco Cilurzo et al., <i>Injectability Evaluation: An Open Issue</i> , 12 AAPS PharmSciTech 604 (2011)	X
2117	<i>Regeneron Pharm., Inc. v. Mylan Pharm. Inc.</i> , 714 F. Supp. 3d 652 (N.D.W. Va. 2024) (“Mylan”)	X

Exhibit	Description	Filed
2118	Jeffrey S. Heier et al., <i>The 1-Year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-Needed After 12-Week Fixed Dosing</i> , 118 Ophthalmology 1098 (2011)	X
2119	RESERVED	
2120	Claudine E. Pang et al., <i>Association Between Needle Size, Postinjection Reflux, and Intraocular Pressure Spikes After Intravitreal Injections</i> , 35 Retina 1401 (2015)	X
2121	Vinicius S. De Stefano et al., <i>Experimental Investigation of Needles, Syringes and Techniques for Intravitreal Injections</i> , 39 Clinical & Experimental Ophthalmology 236 (2011)	X
2122	Jean-Pierre Hubschman et al., <i>Experimental Model of Intravitreal Injection Techniques</i> , 30 Retina 167 (2010)	X
2123	Hussein Hollands, et al., <i>Short-term Intraocular Pressure Changes after Intravitreal Injection of Bevacizumab</i> , 42 Can J. Ophthalmology 807 (2007)	X
2124	Daniel Y. Choi, <i>Sustained Elevated Intraocular Pressures After Intravitreal Injections of Bevacizumab, Ranibizumab, and Pegaptinib</i> , 31(6) Retina 1028 (2011)	X
2125	Third-Party Confidential Transcript	X
2126	Roche, <i>Angiogenesis Highlights</i> (Feb. 16, 2021)	X
2127	U.S. Food & Drug Admin., <i>Inactive Ingredients in Approved Drug Products Search: Frequently Asked Questions</i> , https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-approved-drug-products-search-frequently-asked-questions (last visited June 17, 2026) (“Inactive Ingredient FAQ”)	X

Exhibit	Description	Filed
2128	Mohammed Gabr Kassem, <i>Sunitinib Malate</i> , 37 Profiles of Drug Substances, Excipients, and Related Methodology 363 (2021) (“Kassem”)	X
2129	Xue-qing Wang, <i>Bioavailability and pharmacokinetics of sorafenib suspension, nanoparticles and nanomatrix for oral administration to rat</i> , 419 Int’l J. of Pharmaceutics 339 (2011) (“Wang 2011”)	X
2130	<i>Clinical & Pharmacology & Biopharmaceutics Review(s), Application Number 22-465</i> , Center for Drug Evaluation & Research (2009) (“No. 22-465”)	X
2131	Eylea HD® Highlights of Prescribing Information (Apr. 2026)	X
2132	U.S. Food & Drug Admin., <i>April 2018: Inactive Ingredient Database File</i> , downloaded from https://www.fda.gov/drugs/drug-approvals-and-databases/inactive-ingredients-database-download (last visited June 17, 2026) (“Inactive Ingredient Database”)	X
2133	Excerpt from T.V. Chirila, et al., <i>The Vitreous Humor</i> , Handbook of Biological Properties, 125 (1998) (“Chirila”)	X
2134	Mohab Eldeeb, et al., <i>One-Year Outcomes of Ziv-Aflibercept for Macular Edema in Central Retinal Vein Occlusion</i> , 8 Am. J. Ophthalmology Case Reports 58 (2017) (“Eldeeb”)	X
2135	Tetsuo Hida, <i>Experimental and Clinical Observations of the Intraocular Toxicity of Commercial Cortiosteroid Preparations</i> , 101 Am. J. Ophthalmology 190 (1986) (“Hida”)	X

Exhibit	Description	Filed
2136	J. García-Carmona, <i>Morphological Characteristics and Aggregation of Calcite Crystals Obtained by Bubbling CO₂ through a Ca(OH)₂ Suspension in the Presence of Additives</i> , 130 Powder Tech. 307 (2003) (“García-Carmona”)	X
2137	E.N. Lee et al., <i>Stabilizing Peptide Fusion for Solving the Stability and Solubility Problems of Therapeutic Proteins</i> , 22 Pharm. Res. 1735, 1745 (2005) (“Lee”)	X
2138	J.F. Carpenter et al., <i>Rational Design of Stable Lyophilized Protein Formulations: Theory and Practice</i> , in <i>Rational Design of Stable Protein Formulations</i> 109, 109 (J.F. Carpenter & M.C. Manning eds., 2002) (“Carpenter”)	X
2139	Biochemistry: A Problems Approach, Chapter 2: Amino Acids (2d ed. 1981) (“Biochemistry”)	X
2140	U. Schmidt-Erfurth et al., <i>Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration</i> , 121 Ophthalmology 193 (2014)	X
2141	Regeneron, Regeneron Announces Encouraging Topline Phase 2 Data of High-dose aflibercept in Wet Age-related Macular Degeneration, Regeneron Press Release Details, (Aug. 24, 2021), https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-announces-encouraging-topline-phase-2-data-high-dose	X
2142	Marina Gühlike, <i>Taking Subvisible Particle Quantitation to the Limit</i> , 109 J. Pharm. Sci. 505 (2020) (“Gühlike”)	X
2143	J.G. Gross, <i>Interim Safety Data Comparing Ranibizumab With Panretinal Photocoagulation Among Participants With Proliferative Diabetic Retinopathy</i> , 135 JAMA Ophthalmology 672 (2017)	X
2144	2026.06.09 Email from M. Chacon	X

Exhibit	Description	Filed
2145	2025.09.17 Email from Dr. D'Amico	X

I. Preliminary Statement

“Cross-examination” is the “greatest legal engine ever invented for the discovery of truth.” *California v. Green*, 399 U.S. 149, 158 (1970). The depositions of Alvotech’s declarants discovered the truth: Alvotech’s invalidity case cannot withstand scrutiny.

The Board instituted trial on Alvotech’s Petition, which was predicated on the declarations of two experts: Dr. Robert Falconer, a formulation scientist, and Dr. Donald D’Amico, a clinician. On cross-examination, Dr. Falconer—who offered Alvotech’s sole written-description opinion and opinions essential to Alvotech’s obviousness theories—utterly disavowed nearly every substantive opinion in his declaration when presented with facts he had simply ignored. *Infra* §III.B. He also testified that the declaration he disavowed contained lengthy, substantive opinions that he formed and wrote in “roughly 6 or 8 hours” on the same day that he signed his report, while also presenting at a scientific conference, attending other presentations, and then traveling home. Ex.2046, 22:9-24:17, 217:3-221:21.

Dr. D’Amico fared no better. After confirming his obviousness analysis was premised on hindsight, Ex.2053, 37:15-39:13, he admitted his declaration “accidentally conveyed to the [B]oard that there was better evidence for [his] opinion than [he] actually h[ad]” and that certain critical statements at the heart of his opinions were “inaccurate as written.” Ex.2053, 374:21-376:6. His material

misstatements regarding formation of his opinions, now revealed by contested discovery, gravely undermine his credibility. His haphazard reliance on Dr. Falconer’s abandoned opinions, inconsistent testimony, and admitted overstatements leave no doubt his declaration reflects the opinions of Alvotech’s attorneys, not the POSA. *Infra* §III.C.

Alvotech’s case crumbled under the crucible of cross-examination, and Alvotech is bound to the Petition’s discredited evidence and argument. While trials typically involve a battle of experts, this case is unique: both sides’ experts are aligned against Alvotech’s Petition, agreeing that the patent is adequately described, and that the foundation of Alvotech’s obviousness case is wrong. The Board should join Alvotech’s experts in confirming the validity of all challenged claims.

II. Background

Regeneron’s scientists invented aflibercept, the fusion protein in Eylea[®] and Eylea HD[®]. Aflibercept is a “VEGF antagonist” or “VEGF trap” because it binds vascular endothelial growth factor (VEGF) before VEGF can stimulate blood-vessel growth. *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 127 F.4th 896, 903 (Fed. Cir. 2025); *Regeneron Pharm., Inc. v. Mylan Pharm. Inc.*, 714 F. Supp. 3d 652, 679-80 (N.D.W.Va. 2024) (“*Mylan*”); Ex.1050, 9; Ex.2052, ¶¶51-53. Unlike antibodies or antibody fragments, aflibercept is a fusion protein—a synthetic mashup that combines portions of multiple proteins, including VEGF receptors. Ex.2051, ¶78;

Ex.2052, ¶53. Eylea was the first fusion-protein ophthalmic drug product. *Mylan*, 737.

A. Eylea and Eylea HD

Regeneron's Eylea contains 2 mg aflibercept in a 40-mg/ml formulation administered in a 50-microliter (µL) intravitreal volume. Ex.1050, 9. Approved in 2011, Eylea became a leading ophthalmic anti-VEGF therapy by achieving safety and efficacy comparable to ranibizumab with less frequent maintenance dosing. Ex.2052, ¶¶127-130. Eylea was "revolutionary," "became the leading medicine in its class," and "enabled a major change in the treatment of ophthalmic disease[s]" that can otherwise lead to blindness. *Mylan*, 746-47; Ex.2052, ¶130.

U.S. Patent 12,168,036 discloses and claims Eylea HD, which strove to meet patient need for effective treatment with fewer injections. Ex.2052, ¶¶139-142. It delivers 8 mg aflibercept—four times Eylea's dose—in a 70-microliter injection volume, using a 114.3-mg/ml aflibercept formulation. Ex.2007, 1. FDA approved Eylea HD in 2023, and its label permits dosing once every 8 to 16 weeks after initial loading doses. Ex.2007, 1; Ex.2035, 6; Ex.2052, ¶¶140-142. Alvotech seeks to make a proposed biosimilar to Eylea HD. Ex.2030.

B. Other Attempts at Extended Dosing with Anti-VEGF Products

Eylea HD was not one of many successes. The field had long sought anti-VEGF products that could reduce injection burden without sacrificing safety or

efficacy, but other extended-dosing efforts either failed because of safety concerns or followed a different development path.

Abicipar. Allergan developed abicipar “to help fulfill the unmet need for a long-acting anti-VEGF that decreases the treatment burden for patients with nAMD.” Ex.2022, 1036. FDA refused approval after abicipar caused unfavorable intraocular inflammation rates. Ex.2008; Ex.2031; Ex.2052, ¶¶135-136.

Brolucizumab. Novartis developed brolucizumab to reduce treatment burden using a lower-molecular-weight molecule allowing higher molar dosing than prior therapies. Ex.2024, 90; Ex.2052, ¶137. But brolucizumab exhibited higher intraocular inflammation than aflibercept, Ex.2024, 92, and Novartis later discontinued multiple trials following inflammation and vision-loss, Ex.2032, 2; Ex.2013; Ex.2052, ¶137.

Vabysmo. Vabysmo, approved in 2022, took a different approach to extending treatment intervals: its active protein antagonizes both VEGF and angiopoietin-2 and is administered as a 6 mg dose, lower than Eylea HD’s 8 mg dose. Ex.2026, 1.

Lucentis. Genentech’s Lucentis (ranibizumab) is an anti-VEGF antibody fragment approved at 0.5- and 0.3-mg doses in 10- and 6-mg/ml formulations. Ex.1055, 1; Ex.2052, ¶¶87, 90. Genentech also tested delivering a four-fold higher 2-mg dose in the same 50-microliter intravitreal volume. Ex.2014, 1-2. That higher-

concentration effort failed: it caused ocular inflammation and development ended. Ex.2015, 2040:23-2042:12; *Mylan*, 737-38. Genentech explored 2 mg ranibizumab again in the HARBOR trial, Ex.2052, ¶¶91-92, but the study concluded that quadrupling dose “did not show any clinically meaningful difference in efficacy, durability, or safety,” causing Genentech to abandon its high-dose anti-VEGF product yet again. Ex.1026, 2190; Ex.2052, ¶¶91-95.

III. Procedural History

A. All of Alvotech’s Arguments Depend on Dr. Falconer, or Dr. Falconer and Dr. D’Amico in Combination

On March 3, 2026, the Board instituted Alvotech’s Petition, which depends on the declarations of Drs. Falconer, a formulation scientist, and D’Amico, an ophthalmologist.

Ground	Claims	Basis
1	1, 4-38	Obviousness over Vitti, Australian Eylea Label, Larson.
2	1, 4-38	Obviousness over Furfine, Dix, Australian Eylea Label, Fiedler, Larson.
3	1-38	Lack of written description.
4	2-3	Obviousness over Vitti, Australian Eylea Label, Larson, 2011 Eylea Clinical Review.
5	2-3	Obviousness over Furfine, Dix, Australian Eylea Label, Fiedler, Larson, and 2011 Eylea Clinical Review.

Alvotech’s written-description challenge depends on Dr. Falconer’s testimony alone. Each of Alvotech’s obviousness grounds relies on *both* Dr.

D’Amico’s and Dr. Falconer’s opinions in critical respects. If the Board declines to credit the opinion of either expert on relevant points, the obviousness grounds fail.

Regeneron deposed Dr. Falconer (Ex.2046) and Dr. D’Amico (Ex.2053). Their depositions revealed a concerning lack of care and independence in preparing their declarations and a misunderstanding of the relevant legal standards, the ’036 patent, and the prior art as a whole.

B. The Board Should Not Credit Dr. Falconer’s Opinions

On cross-examination, Dr. Falconer disavowed nearly every substantive opinion in his declaration. This is perhaps unsurprising, given his testimony that all his opinions regarding dose and administration volume were formed over a 6-8 hour window on the day he signed his declaration. That was a very busy day for Dr. Falconer—he also presented at a conference in Melbourne, attended other presentations, and flew home. Ex.2046, 22:9-24; 219:20-221:21.

The degree to which Dr. Falconer contradicted at deposition his sworn declaration is, charitably put, exceptional. It must be read in full to be believed. His deposition revokes most of the opinions expressed in his declaration and casts doubt on the reliability of any that remain. Select examples include:

Declaration (Ex.1004)	Deposition (Ex.2046)
<p><u>Paragraph 269:</u></p> <p>“[T]he ’036 Patent specification discloses only a small number of species that actually achieve the required viscosity[.]”</p>	<p><u>179:8-13</u></p> <p>Q. “There are numerous examples in the patent, both in the figures and in the written description portion describing formulations of aflibercept with at least 100 mgs per ml and viscosities of about 5 to 15 centipoise, correct?</p> <p>A. Correct.”</p> <p><u>167:19-23</u></p> <p>Q. “[T]he ’036 patent inventors provided extensive data on viscosities of particular high concentration aflibercept formulations in the patent, correct?</p> <p>A. Correct.”</p>
<p><u>Paragraph 276:</u></p> <p>“[T]he limited number of formulations disclosed in the ’036 Patent specification that achieve the claimed viscosity of 5-15 cP at 20° C fails to provide adequate written description support for the full scope of the claims[.]”</p>	<p><u>179:5-18</u></p> <p>Q. “[T]he description of those formulations [in the patent] provides adequate written description support for claims claiming at least 100 mgs per ml of aflibercept with 5 to 15 centipoise viscosity, correct?</p> <p>A. Correct.”</p>

	<p><u>193:18-194:7.</u></p> <p>Q. “[Y]ou don’t have an opinion that claim 31 lacks written description support, correct?</p> <p>A. Correct.</p> <p>Q.[Y]ou don’t have an opinion that claim 35 lacks written description support, correct?</p> <p>A. Correct.”</p>
<p><u>Paragraph 178:</u></p> <p>“[I]n light of Vitti, a skilled formulator would have reasonably expected to succeed in optimizing for and obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 114.3 mg/mL of aflibercept.”</p>	<p><u>55:21-56:3:</u></p> <p>Q. The POSA would not have a reasonable expectation of success based upon Vitti in achieving aqueous formulations suitable for intravitreal administration containing at least 100 mgs per ml of a VEGF-inhibiting fusion protein falling within the scope of Vitti’s VEGF antagonist definition, correct?</p> <p>A. That’s correct because the definition is so broad. Yes.”</p>
<p><u>Paragraph 177:</u></p> <p>“[G]iven the teachings in Vitti regarding stable aqueous pharmaceutical formulations for</p>	<p><u>73:14-17</u></p> <p>Q. “Vitti doesn’t teach that aqueous formulations of aflibercept at 114.3 mgs per ml are stable, correct?</p> <p>A. Correct.”</p>

intravitreal injection containing up to 115 mg/mL of aflibercept”	
<p><u>Paragraph 191:</u></p> <p>“Furfine teaches stable aflibercept formulations containing at least 100 mg/mL of aflibercept.”</p>	<p><u>76:24-77:17</u></p> <p>Q. “You stated in paragraph 191 of your declaration that Furfine teaches stable aflibercept formulations containing at least 100 mgs per ml of aflibercept, correct?</p> <p>A. That’s what it says here, yes.</p> <p>Q.So this statement’s not accurate insofar as it’s suggesting that Furfine teaches greater than 100 mgs per ml of aflibercept, right?</p> <p>A. Yes. Furfine in isolation does not teach over 100.</p> <p>Q. Okay. So do you retract this statement in your declaration regarding Furfine?</p> <p>A. Yes. I think preferred wording would be up to.”</p>

C. The Board Should Not Credit Dr. D’Amico’s Opinions

Dr. D’Amico’s deposition likewise demonstrated a lack of care and independence in providing written and oral sworn testimony. As Board-ordered discovery later revealed, Dr. D’Amico repeatedly misrepresented the manner in

which he formed his opinions, evidently seeking to elide either an improbable slapdash effort or a stunning lack of independence.

Dr. D’Amico’s declaration represents that, in forming his opinions, he had relied on a conversation with Dr. Falconer in June 2025, three months before signing his declaration. Only after receiving discovery requests directed to the inconsistency between that date and Dr. Falconer’s testimony that he spoke to Dr. D’Amico precisely once, on the day before both doctors signed their declarations, Alvotech’s counsel averred that Dr. D’Amico’s declaration contained a “typo[.]” Ex.2144. This “typo[.]” “confirm[ed]” that Dr. D’Amico had not, in fact, had three months to consider carefully his conversation with Dr. Falconer as he formed his opinions. *Id.* He had a day. *Id.*

Even setting aside that material misrepresentation, Dr. D’Amico egregiously misrepresented the process by which he formed and prepared his opinions. For example, he testified repeatedly that he reviewed Dr. Falconer’s report in full before even “putting pen to paper” on his own. Ex.2053, 27:2-21. He must be a fast reader and an even faster typist. As contested discovery revealed, Dr. D’Amico received Dr. Falconer’s 113-page declaration at 4:15 PM on September 17, 2025. Ex.2145. A mere *34 minutes later*, Dr. D’Amico provided signature authority for his own 181-page declaration (which includes 46 citations to paragraphs of Dr. Falconer’s

declaration). Ex.2145; Ex.1003; Ex.2053 at 62:15-18 (testifying that he verified all citations).

This is no “gotcha.” Dr. D’Amico’s insouciant attitude towards sworn testimony produced an unreliable declaration with admittedly incorrect foundational opinions. For example, all challenged claims recite high-dose aflibercept—at least about 8 mg, four times the 2-mg dose approved as of the priority date. Dr. D’Amico thus predicates his obviousness conclusions on his opinions that the POSA expected an 8-mg dose to (1) have a longer duration of effect than lower doses (without being any less effective), and (2) be safe. As Dr. D’Amico testified in his declaration:

43. Regeneron conducted a series of clinical trials supporting the safety and efficacy of aflibercept. *As it relates to the issues I have been asked to opine on, these clinical trials demonstrate that increasing the dose of aflibercept would prolong its duration of action in the eye resulting in a reduction of the frequency of injections for patients.* EX1039 at 1182. The clinical trials also supported that there was no likely risk of drug toxicity with increasing the dose of aflibercept to 8 mg. EX1058 at 20-21. I discuss relevant clinical trials below.

Ex.1003, ¶43.

But at deposition, Dr. D’Amico conceded these statements “are inaccurate as written.” Ex.2053, 389:16-390:1. He agreed that his statement regarding clinical benefit (*italicized*) was “inaccurate” because the referenced aflibercept trials do not

demonstrate anything regarding increased duration of action. Ex.2053, 388:6-390:1. Indeed, Dr. D’Amico *did not even review* the full results of the referenced aflibercept trials (VIEW 1 and VIEW 2). Ex.1003, ¶12.¹ He relied instead on an earlier-published review paper containing only snippets of the relevant data and then conceded that he overstated even that author’s interpretation. Ex.2053, 388:6-390:1.

Dr. D’Amico also confirmed that his statement in paragraph 43 (underlined) that clinical trials supported an expectation of safety is false, because the aflibercept “clinical trials” he relied on were not clinical trials at all—they were animal studies. Ex.2053, 373:4-376:6. Thus, Dr. D’Amico agreed that his Declaration “conveyed to the [B]oard that there was better evidence for [his] opinion than [he] actually had[.]” Ex.2053, 373:4-376:6.

Concerns regarding Dr. D’Amico’s testimony could fill this brief. Selective citations to incomplete data and a transparently hindsight-driven approach infect his entire analysis. The Board should not credit his opinions.

IV. U.S. Patent 12,168,036

A. Specification

Developing a “therapeutically useful liquid formulation” is a difficult, uncertain endeavor that requires carefully selecting—and balancing—active and

¹ Dr. D’Amico’s materials considered do not include Heier 2012 (Ex.2090) or Schmidt-Erfurth 2014 (Ex.2140), which published the full results of VIEW 1 and 2.

inactive ingredients to achieve “a functional and stable delivery vehicle.” Ex.1001, 1:42-45. That is especially true for protein and antibody formulations, which “have long presented challenges to drug developers and manufacturers, as antibody activity and administration typically require a pharmaceutically acceptable potency, osmolality, protein stability, viscosity, and proper pH.” *Id.*, 1:46-50. “These challenges are exacerbated when the antibody is at higher concentrations in the formulation, for example, beyond 20 to 40 mg/ml, the concentration of most pharmaceutically sold antibodies.” *Id.*, 1:50-54.

High-concentration formulations offer potential benefits, including “shorter injection times, smaller injection volumes, lower frequency of antibody administration, and more efficient manufacturing and storage utility.” *Id.*, 1:56-58. However, “high concentration antibody and protein formulations often contend with increased protein aggregation and viscosity, which results in lower overall antibody or protein potency, and lower manufacturing and poorer storage stability.” *Id.*, 1:61-65. It is no surprise that “few such pharmaceutically acceptable formulations have been developed” and that “high concentration, high stability, antibody and protein formulations that include the proper potency, stability, viscosity, osmolality and pH” have proved difficult to attain. *Id.*, 1:65-2:4; *supra* §II.B.

Treating angiogenic eye disorders historically required “monthly or bi-monthly” intravitreal injections, but such frequent “injections represent a significant

treatment burden on patients, caregivers, and physicians.” Ex.1001, 51:19-25. Accordingly, “[t]here is a pressing need for more effective and durable therapies in clinical practice.” *Id.*, 51:25-26. The ’036 patent teaches that increasing protein concentration could help achieve increased durability, reduced injection frequency, and a reduced risk of intraocular pressure increases associated with higher injection volumes. *Id.*, 2:10-14, 2:25-33.

But higher concentrations may increase aggregation and viscosity, “making the formulations difficult for intravitreal injection,” *Id.*, 20:34-38, 1:61-65. “Preventing aflibercept from aggregating and coming out of solution is especially important in the context of intravitreal injections,” as “[f]orcing protein solutions through a narrow-bore needle creates shear stress, which can cause a protein to aggregate and come out of solution.” *Mylan*, 707 ((quoting and citing Ex.2015, 472:21-473:8, 577:10-579:10 (Trout), 476:2-24 (Furfine), 1680:6-11 (Graham)). “A protein coming out of solution can lead to several potential problems, including protein inactivation, inflammation, and even adverse immune responses.” *Id.* Increased viscosity results from higher concentrations and can make intravitreal injections—administered through narrow-bore needles—difficult and less safe. Ex.1001, 13:33-39; Ex.2015, 476:2-477:24.

The inventors overcame these difficulties, achieving stable, high-concentration, low-viscosity aflibercept formulations. Ex.1001, 2:20-40, 13:20-41,

20:31-41, 38:26-40:11, 42:14-22. One such formulation is Eylea HD, Ex.2007, 1, and the specification discloses several dozen others. Ex.1001, 23:22-28:19. Figure 3B discloses nine formulations with 155 mg/ml aflibercept. *Id.*, 9:46-10:4, 38:32-54, 39:15-40:11, Fig.3B; Ex.2051, ¶¶44, 244. Figure 3C discloses sixteen formulations with aflibercept concentrations from 10-160 mg/ml. Ex.1001, 10:5-8, 38:55-67, Fig.3C; Ex.2051, ¶245. Figure 5 discloses sixteen formulations with aflibercept concentrations from 10-170 mg/ml. Ex.1001, 10:24-29, 42:17-22, Fig.5; Ex.2051, ¶246. Figure 9 discloses twelve formulations with 140 mg/ml aflibercept. Ex.1001, 10:45-11:26, 50:15-45, Fig.9; Ex.2051, ¶¶47, 247. With few exceptions addressed below and in Dr. Trout's declaration, the formulations achieved the claimed viscosity. Ex.2051, ¶¶244-253. The '036 patent discloses at least 31 distinct formulations with 100 mg/ml aflibercept or higher, viscosities of less than 15 cP, and over a dozen different ingredients and multiple concentrations thereof. Ex.1001, 9:46-11:26, 38:47-40:14, 42:14-22, 50:15-45, Figs. 3B, 3C, 5, 9; Ex.2051, ¶¶244-253.

B. Prosecution History

The Examiner rejected as inadequately described the original claims reciting “administering...at least about 8 mg of a VEGF receptor fusion protein,” Ex.2001, 2, concluding that “the claim recites a high concentration of a VEGF receptor fusion protein without any recitation of the elements of the composition that permit such a

high concentration of the protein.” Ex.2001, 230-31.

Regeneron amended the claims to recite a volume of about 100 microliters or less, a concentration of at least 100 mg/ml, and a viscosity of about 5-15 cP, Ex.2001, 289, explaining that “[t]he formulation specified in the amended claims is optimal for delivery of at least 8 mg of VEGF receptor fusion protein to the vitreum in terms of several interrelated factors: protein concentration, injection volume[,] and viscosity.” Ex.2001, 295. All three interrelated factors, Regeneron detailed, are critical to safe and effective intravitreal administration. Ex.2001, 295-296. Despite the difficulties of increasing concentration to achieve smaller injection volumes while avoiding increasing viscosity and aggregation, the inventors successfully developed formulations meeting the claimed criteria. Ex.2001, 296. In “Figures 3B, 3C[,] and 5...the viscosities of several formulations including a variety of excipients were measured to be within the 5-15 cP range specified in the claims.” *Id.* Thus, “a representative number of species encompassed by the claims have been disclosed,” and “the amended claims are fully described.” *Id.* The Examiner agreed, withdrew the §112 rejection given Regeneron’s amendment and “persuasive arguments,” and allowed the claims. Ex.2001, 306, 308.

The Examiner also considered Vitti (Ex.1007), Furfine (Ex.1005), Dix (Ex.1006), and Fiedler (Ex.1011)—each in Alvotech’s obviousness Grounds. Ex.2001, 236-37, 240, 251, 324, 371, 396-97, 400, 411, 527. The Examiner issued

no rejections based on these or other references.

C. Challenged Claims

Claim 1 requires a “method for treating an angiogenic eye disorder” comprising administering an intravitreal injection with the following limitations as relevant here:

- at *least about 8 mg* of a VEGF receptor fusion protein (e.g., aflibercept);
- in a volume of about 100 μL or less;
- at a concentration of at least 100 mg/ml;
- with a viscosity of about 5-15 centiPoise (cP) at 20° C.

Ex.1001, claim 1. Dependent claims 2-30 add treatment outcomes, viscosities, formulation components, and eye disorders.

Claim 31 tracks the Eylea HD composition. Ex.2007, 1. This formulation achieves a viscosity of about 5-15 cP, despite its high protein concentration. Ex.1001, 20:13-30, 10:5-8, 38:55-67, Figs.3A-3C. Claims 32-34 depend from claim 31, reciting particular eye disorders.

Independent claim 35 recites additional aflibercept formulations at a concentration range of 103-126 mg/ml—encompassing the 114.3 mg/ml Eylea HD concentration—which achieve 5-15 cP viscosity. Ex.1001, claim 35. Claims 36-38 depend from claim 35 and recite particular eye disorders.

V. Person of Ordinary Skill

Regeneron applies Alvotech's POSA definition. Pet.10-11.

VI. Alvotech Cannot Prove Obviousness

A. Legal Standards

Alvotech bears the burden of proving, by preponderant evidence, that the POSA would have been motivated to combine the prior-art teachings to achieve the claimed invention, with a reasonable expectation of success. *In re Cyclobenzaprine Pat. Litig.*, 676 F.3d 1063, 1068-69 (Fed. Cir. 2012).

Hindsight is prohibited. *KSR Int'l v. Teleflex*, 550 U.S. 398, 421 (2007); *Otsuka Pharm. v. Sandoz*, 678 F.3d 1280, 1296 (Fed. Cir. 2012). Obviousness cannot be proved by starting from the claimed invention and working backwards to identify each limitation in the prior art. *Ortho-McNeil Pharm. v. Mylan Labs.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

Obviousness likewise cannot be demonstrated by cherry-picking prior-art disclosures. *Arctic Cat v. Bombardier Recreational Prods.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017) (“[I]t is error to fail to consider the entirety of the art.”). The art must be considered as a whole, including disclosures that teach away from the invention. *Polaris Indus. v. Arctic Cat*, 882 F.3d 1056, 1069 (Fed. Cir. 2018); *DePuy Spine v. Medtronic*, 567 F.3d 1314, 1326-27 (Fed. Cir. 2009) (“An inference of nonobviousness is especially strong where the prior art's teachings undermine the

very reason being proffered as to why a [POSA] would have combined the known elements.”).

A reference teaches away if the POSA, “upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *Millennium Pharms. v. Sandoz*, 862 F.3d 1356, 1366 (Fed. Cir. 2017). “Obviousness may be defeated if the prior art indicates that the invention would not have worked for its intended purpose or otherwise teaches away from the invention.” *Meiresonne v. Google*, 849 F.3d 1379, 1382 (Fed. Cir. 2017). Prior-art preferences can negate obviousness even without teaching away. *Polaris*, 882 F.3d at 1069; *Apple v. Samsung*, 839 F.3d 1034, 1051 n.15 (Fed. Cir. 2016) (en banc).

If a prior-art reference discloses the same variable as claimed, but as a range of values, “and the claimed invention falls within that range, a relevant inquiry is whether there would have been a motivation to select the claimed composition from the prior art ranges.” *Allergan v. Sandoz*, 796 F.3d 1293, 1304-05 (Fed. Cir. 2015). Crucially, the prior art must disclose a range for the same limitation claimed—otherwise, the range inquiry does not apply. *ModernaTx v. Arbutus Biopharma*, 18 F.4th 1364, 1373-74 (Fed. Cir. 2021). Additionally, “the disclosure of a range is not a disclosure of the endpoints of the range or other discrete points within the range.” *UCB v. Actavis Labs.*, 65 F.4th 679, 688 (Fed. Cir. 2023).

Even where applicable, disclosed ranges can render a value obvious only where (1) “the optimized variable is a result-effective variable,” *In re Applied Materials*, 692 F.3d 1289, 1295 (Fed. Cir. 2012), and (2) the disclosed ranges are not “so broad as to encompass a very large number of possible distinct compositions, such that they do not teach any specific amounts or combinations,” *Allergan*, 796 F.3d at 1305. The analysis’ guiding premises “are materially the same as the basic factual inquiries of the normal full obviousness analysis (motivation to combine or modify and expectation of success).” *Janssen Pharm. v. Teva*, 141 F.4th 1367, 1377 (Fed. Cir. 2025). “[E]vidence of teaching away, unexpected results, and other pertinent secondary considerations” can rebut a finding that a range renders a value within it obvious. *Allergan*, 796 F.3d at 1305.

B. Ground 1: Alvotech Fails To Demonstrate Obviousness over Vitti, AU Label, and Larson

1. Claims 31-38

Ground 1 asserts obviousness over Vitti, AU Label, and Larson. Pet.42-48. Claims 31-38 recite a method of treating an angiogenic eye disorder comprising administering (1) about 8 mg aflibercept, (2) at concentration of about 114.3 mg/ml (claim 31) or 103-126 mg/ml (claim 35), (3) in a volume of about 70 microliters, and (4) with a viscosity of about 5-15 cP. Ex.1001, claims 31, 35. Ground 1 rests on selective extraction of data points from the prior art, hindsight-driven math, and a

failure to account for significant gaps between the prior-art disclosures and the claimed invention.

Alvotech contends the POSA would have been motivated to combine Vitti, AU Label, and Larson to develop an 8-mg aflibercept formulation because such a high dose would be safe and longer-lasting, thereby requiring fewer injections. Pet.19-22. Not so. The prior art in fact taught that increasing dose was unlikely to improve duration of effect, Ex.2052, ¶¶175-183, 195-202 and presented safety concerns. *id.*, ¶¶143-203. But even a general desire for fewer injections does not provide a reason to select the specific combination of claimed parameters. The only overlap between Vitti and AU Label is 2 mg aflibercept at 40 mg/ml in a 50-μL volume—not the high-concentration, high-dose formulations of claims 31-38. Ex.1007, ¶¶127, 198-201; Ex.1009, 2, 29; Ex.2052, ¶¶150, 165-174. To reach the claimed 8-mg dose at 114.3 mg/ml in a 70-μL volume, the POSA would need to: (1) quadruple the dose from 2 to 8 mg, despite safety concerns and a lack of evidence of any clinical benefit; (2) nearly triple the 40 mg/ml aflibercept concentration in all of Vitti's working examples; (3) increase the injection volume by 40%; and (4) achieve a viscosity of 5-15 cP at 20°C—all without any accompanying teaching or suggestion. Ex.1007, ¶¶198-201; Ex.1009, 35. Alvotech cannot prove any of those four elements, much less *all* four, as required to prevail on obviousness. Alvotech's argument defies the contemporaneous art, which is why its experts declined to

defend its premises and admitted to using hindsight at every turn. Ex.2053, 37:7-39:13 (Dr. D’Amico searched prior art for claim limitations, and “knew to search for those things because they’re written in the claims of the ’036 patent.”), 237:2-34 (considering “high dose Eylea,” as “described in the ’036 patent,” and the “work of th[e] inventors” in forming his obviousness opinions, concluding “what the inventors disclosed in th[e] [’036] patent[] made it more likely that the claims were obvious.”).

a. The POSA Would Not Select 8 mg

Alvotech relies on AU Label (Ex.1009) and Vitti (Ex.1007) as allegedly teaching an 8-mg aflibercept dose. Nothing in these references would have led the POSA to pursue that dose. The only path to an 8-mg dose is hindsight.

i. The POSA Lacked Motivation for 8 mg.

Alvotech’s art does not teach the POSA to use an 8-mg aflibercept dose. As of May 2018, clinicians had been using the FDA-approved, 2-mg dose successfully for seven years. Ex.2052, ¶130. As Regeneron’s clinical expert, Dr. Neil Bressler, explains, to have been motivated to depart from that successful paradigm, the POSA would have needed to believe that (1) there was some clinical benefit to be gained from 8 mg, Ex.2052, ¶¶175-183, and (2) 8 mg would be safe, Ex.2052, ¶¶195-202. Neither was true. Ex.2052, ¶¶175-202.

1. Vitti Did Not Motivate the POSA To Select 8 mg

Alvotech asserts that Vitti motivated the POSA to select 8 mg aflibercept. Pet.28-29. Dr. D’Amico repeatedly disagreed, confirming that *his* “primary impetus” was the Australian label. Ex.2053, 324:14-23, 327:14-17 (“Q. So is [motivation] *partially* based on Vitti? A. The initial impetus is based on the Australian label.”), 332:5-333:18 (“[T]he target dose is established by the Australian label.”).

Alvotech nevertheless argues that the POSA would have selected 8 mg aflibercept because Vitti discloses “0.05 mg to about 10 mg of a VEGF antagonist (e.g., aflibercept).” Pet.28; Ex.1007, ¶139. Not so. Dr. D’Amico’s declaration does not even reference this disclosure in connection with the 8-mg limitation, Ex.1003, ¶¶195-198, 245, 251, and for good reason—it contains nearly 1000 discrete aflibercept doses in 0.01-mg increments, Ex.2052, ¶165. No presumption of obviousness applies where, as here, the prior-art range is “so broad as to encompass a very large number of possible distinct compositions.” *Genetics Inst. v. Novartis*, 655 F.3d 1291, 1306 (Fed. Cir. 2011); Ex.2051, ¶¶102, 115-124, 132; Pet.13-14; Ex.1003, ¶¶128-134. Nothing in Vitti directs the POSA to 8 mg among the myriad options; Vitti’s examples use 2 mg, 40 mg/ml aflibercept, just as the POSA would have done. Ex.1007, ¶¶197-217, 227-308; Ex.2052, ¶173.

Recognizing its problem, Alvotech resorts to blatantly hindsight-driven math. First, it points to Vitti’s supposed “preferred embodiments” of 80, 90, and 100

mg/ml—while ignoring eleven, equally “preferred” and lower-concentration embodiments in the same sentence. Pet.29; Ex.1007, ¶94. Next, Alvotech multiplies those concentrations by a 100-μL volume to calculate doses of 8, 9, and 10 mg. Ex.2053, 331:6-19; Ex.1003, ¶¶196-197; Pet.29-30. Dr. D’Amico selected the 100-μL upper limit for intravitreal injections, notwithstanding Alvotech’s argument that the POSA would not use that volume. Ex.1003, ¶197. Of course, had the POSA multiplied these concentrations by 70 μL (which Alvotech says the POSA would have selected), the calculated doses would be *less* than 8 mg. Ex.2052, ¶¶170-171. Alvotech thus asserts the POSA would have (1) cherry-picked concentrations from Vitti that the POSA would *not* use, Pet.29), (2) multiplied those concentrations by a volume from Vitti the POSA *also* would not use, Pet.29), all to arrive at a “disclosure” of three doses, including the claimed 8 mg. Then, Alvotech asserts, the POSA would have reversed the process by (3) taking the just-calculated doses, (4) disregarding the concentration/volume assumptions that produced them, and (5) somehow back-calculating a concentration of 114.3 mg/ml and volume of 70 μL. Pet.43-45.

Unsurprisingly, Dr. D’Amico became “totally lost” when discussing these calculations that his declaration called “basic and routine mathematics.” Ex.1003, ¶197; Ex.2053, 314:8-323:15. He ultimately agreed that “Vitti discloses a very

broad range of doses” that can be “calculate[d] using the kind of math” in his declaration, and “within that somewhere is 8 milligrams.” Ex.2053, 333:20-25.

Moreover, Alvotech ignores that Vitti’s approach to extended dosing entailed co-administering angiopoietin-2 (Ang-2) inhibitors with VEGF antagonists, and Vitti’s co-formulation studies all used prior-art 40 mg/ml aflibercept, not the higher concentrations Alvotech plucks from ranges with hindsight. Ex.1007, Abstract, ¶¶15, 127, 198-201; Ex.2052, ¶¶172-173. Vitti does not provide motivation for 8 mg aflibercept. Ex.2052, ¶¶165-174.

2. The Overdosage Section of AU Label Provides No Motivation To Select 8 mg

AU Label did not motivate the POSA to use an 8-mg aflibercept dose. The experts *agree* that the Australian “Product Information” for **2 mg** Eylea® instructs clinicians to do exactly what one would expect—administer a **2 mg** dose of Eylea® (aflibercept). Ex.1009, 29; Ex.2053, 369:24-371:4 (Ex.1009 motivates POSA to administer 2 mg); Ex.2052, ¶¶149-151. The Label is explicit: “The recommended dose for EYLEA is **2 mg** aflibercept, equivalent to an injection volume of 50 µL,” and provides efficacy and safety data, including adverse event summaries, from eight, phase III clinical trials testing **2 mg**. Ex.1009, 8-29; Ex.2052, ¶¶152-164.

Nevertheless, Alvotech argues, the POSA would have pursued an 8-mg dose by taking guidance *not* from the Dosage and Administration section, *nor* from associated clinical trial and adverse event data sections, but instead from the

“Overdosage” section—which directs clinicians to call the Poisons Information Centre if 8 mg is administered, and warns of “increased injection volume and subsequently ... increased intraocular pressure.” Ex.1009, 35; Pet.30.

This is not motivation. It is a warning. Alvotech counters that the Label describes these “isolated cases” of accidental overdoses as “generally well tolerated.” Pet.16, 30. According to Dr. D’Amico, that means the patients “did not lose the eye. They did not have rip-roaring retinitis. They did not have vision decrease.” Ex.2053, 404:25-405:8. Dr. Bressler agrees but explains these outcomes are a far cry from “safety.” Ex.2052, ¶151. Despite the total absence of *any* quantifiable information, Dr. D’Amico testified that the Label provides “a high level of data” for 8 mg aflibercept. Ex.2053, 406:23-407:15.

In contrast, when asked whether literature reporting an accidental overdose of six patients with another intraocular drug would provide a reason to administer the higher, overdosed amount, he answered, “No” and “Not at all.” Ex.2053, 132:25-133:22.² The POSA would have viewed the Label’s “well tolerated” overdoses

² Ex.2044 reports six patients with six months of detailed clinical follow-up (more information than AU Label). Ex.2044, 460-61. Nevertheless, Dr. D’Amico discounted Ex.2044 because he was not familiar with the clinicians reporting the overdose or how they verified the overdose quantity, and the paper was not “a more rigorously conducted trial with ... multiple observations.” Ex.2053, 140:12-143:25. All these facts are true of AU Label. Ex.2053, 400:22-411:5.

precisely the same way and would not have pursued an untested strategy likely to involve Poison Control. Ex.2052, ¶¶153-164.

3. Prior Art Taught That Increasing Dose Did Not Provide Patient Benefit

Alvotech asserts that the POSA generally was motivated to use a high dose of aflibercept (“at least about 8 mg”) because it was expected to provide longer duration of action, thereby reducing injection burden. Pet.20-22. The prior art taught the opposite. Ex.2052, ¶¶175-185, 193.

Alvotech’s durability theory relies principally on a single review paper—Stewart 2012 (Ex.1039). Pet.21-22, 24. Stewart summarizes excerpts of a high-dose ranibizumab study (HARBOR, full results in Ex.1026) and aflibercept phase I, II, and III trials. Ex.1039, 1179-82; Ex.2052, ¶¶92-95, 186-191. Stewart contains Alvotech’s favorite statement: “Both trials suggest, but do not prove, that increasing the dose of a drug prolongs its duration of action (durability).” Ex.1039, 1182. This is the same statement Dr. D’Amico confirmed he had reported “inaccurate[ly]” in his declaration. *Supra* §III.C.

Stewart’s reference to “[b]oth trials” is to the VIEW aflibercept phase III trials, and the HARBOR ranibizumab trial. Ex.1039, 1182. Alvotech’s problem is

that Stewart predated the publication of the results from those trials.³ Two years later, the HARBOR results published. They showed exactly the *opposite* of what Stewart predicted: Over two years, the four-fold higher (2.0 mg) dose of ranibizumab “**did not show any clinically meaningful difference in efficacy, durability, or safety compared with the 0.5 mg ranibizumab dose.**” Ex.1026, 2190. Remarkably, the Petition and Dr. D’Amico’s declaration omit any reference to this crucial disclosure. The POSA would not have overlooked it, and would have agreed with the HARBOR authors’ conclusion, just as Dr. D’Amico did at deposition. Ex.2052, ¶¶186-191; Ex.2053, 392:12-393:9.

Dr. D’Amico retreated to argue that the POSA “would be motivated to do things that are not clinically meaningful.” Ex.2053, 265:16-20. That is Alvotech’s only remaining rationale, since both the 1-year and 2-year results of HARBOR taught that *quadrupling* anti-VEGF dose was unlikely to reduce the injection burden. Ex.2052, ¶¶96-106, 186-189.

The other studies Stewart referenced, the VIEW trials, involved no dose higher than 2 mg aflibercept and so could not compare the effects of increasing beyond 2 mg. Ex.2052, ¶¶127-130. Dr. D’Amico did not cite their full results. Ex.1003, ¶12. Dr. D’Amico also ignored Macugen studies suggesting that higher

³ Dr. Stewart cites “data on file” for HARBOR and a Regeneron press release for VIEW. Ex.2052, ¶186; Ex.1039, 1181 n.113, 1182.

anti-VEGF doses can produce worse clinical outcomes. Ex.2052, ¶¶76-82, 192 (citing Ex.2088, 2809-10; Ex.2103, 1707-08).

Most stunningly, Dr. D’Amico ignored the publications of aflibercept’s phase II (CLEAR-IT 2) results. Ex.1003, ¶12. The phase I CLEAR-IT 1 study Dr. D’Amico emphasizes involved fewer participants than CLEAR-IT 2 (21 vs. 159), fewer injections (single vs. multiple) and shorter duration (8 weeks versus 52 weeks), as Dr. D’Amico agreed. Ex.2053, 270:10-271:7, 280:16-22; Ex.2052, ¶¶112-113, 176-77. Moreover, CLEAR-IT 1 did not compare 4 and 2 mg doses. Ex.2052, ¶126; Ex.1034, 2141-47 (reporting 2 and 4 mg collectively), Ex.1035, 581-87 (comparing 4 to 0.15 mg).

CLEAR-IT 2 patients received repeat doses of 0.5, 2, or 4 mg aflibercept. Ex.2089, 1089-90. Dr. D’Amico agreed that a 4-to-2 mg comparison, which Stewart omitted but the full results contain, would be “informative” in the “complicated analysis” of whether increasing aflibercept dose would increase durability—the very premise of his opinions. Ex.2053, 280:16-282:18. Only Dr. Bressler relied upon and formed opinions concerning the full CLEAR-IT 2 results (Ex.2089, Ex.2090). As he explains, CLEAR-IT 2 taught that 4 mg aflibercept did not provide a clinically meaningful improvement over 2 mg. Ex.2052, ¶¶113-126, 180-182. Clinical Review summarizes the aflibercept trial results: “the maximum improvement [was]

achieved at a dose of 2 mg/eye.” Ex.1008, 10, 13; Ex.2052, ¶194. As of 2018, the evidence did not support increasing dose—that idea was dead.

Thus, the Petition’s statement (Pet.24) that “a study regarding aflibercept and another anti-VEGF drug, ranibizumab, reported that a 4-fold increase in dose ‘has a greater effect on its durability than its efficacy’” is simply wrong. Ex.2052, ¶¶186-191. The quoted language comes not from a *study* but from the Stewart *review* article, where it describes “previously published models” in monkeys from a 2005 paper (Ex.2014) that does not involve aflibercept and that Dr. D’Amico did not even bother to review. Ex.1003, ¶¶12, 84-85, 172; Ex.2052 ¶¶108-111; 190-191; Ex.1039, 1182. Alvotech’s stretch for evidence is telling.

4. The Prior Art Did Not Suggest 8 mg Would Be Safe

Nothing in Vitti or AU Label suggested that an 8 mg dose was safe—indeed, the Label explicitly warned of increased intraocular pressure. *Supra* §VI.B.1.a.i.2; Ex.2052, ¶¶153-164. Nor did HARBOR teach that quadrupling the dose of *aflibercept* was safe merely because quadrupling ranibizumab doses did not result in an observed increase in safety issues. Ex.2052, ¶¶96-106, 186-189. As Dr. D’Amico confirmed repeatedly, given that “clinical dosing” “is highly variable and a complicated science in itself,” safety data cannot be extrapolated from one drug to another, even within a class. Ex.2053, 80:5-82:3, 83:13-22. When asked about applying knowledge from increasing doses of ranibizumab to increasing doses of

aflibercept, he explained that “[t]he drugs are different... [T]he safety effects could be different. The effect of higher dosage could be different, etc....” Ex.2053, 418:12-20; Ex.2052, ¶¶131-133, 184-185, 200-202.

Dr. D’Amico relies on a Conference Presentation’s brief reference to CLEAR-IT 1 results. Pet.25; Ex.1003, ¶167. Alvotech asserts that because the maximum tolerated dose had not yet been achieved with 4 mg, the POSA would consider 8 mg clinically safe. Pet.50-51; Ex.1003, ¶167. That is wrong. The maximum tolerated dose is the highest dose that did not cause *unacceptable* or dose-limiting toxicities, Ex.2052, ¶179, an inquiry that does not require the POSA to weigh, as here, increased potential for adverse events against expected therapeutic benefit. By conveying safety concerns but no benefit associated with a high-dose approach, *supra* §§VI.B.1.a.i.2-3, the art guided the POSA away from 8 mg. Ex.2052, ¶¶175-203. Dr. D’Amico initially testified that clinical studies of aflibercept “supported that there was no likely risk of drug toxicity with increasing the dose of aflibercept to 8 mg” but later confirmed that this declaration testimony was inaccurate. *Supra* §III.C. No prior-art clinical trial data for 8 mg aflibercept exists. Ex.2052, ¶¶175-183.

5. Formulation Concerns Discouraged 8 mg

Independently, Alvotech’s 8-mg theory fails for a formulation reason inseparable from dose. At the prior-art 40 mg/ml and 50 mg/ml concentrations, an

8-mg dose requires an intravitreal injection volume above the 100- μ L upper limit; fitting 8 mg within a desirable volume would require high-concentration intravitreal aflibercept formulations that the art did not teach and, as explained below, discouraged. Ex.2051, ¶¶100, 143; Ex.2052, ¶¶69-74; *infra* §§VI.B.1.b-d; *see DePuy Spine*, 567 F.3d at 1326-27. Increasing protein concentration was known to increase aggregation, instability, and viscosity risks, especially for intravitreal products. Ex.2051, ¶¶79-96, 103-105, 133, 152, 181; *infra* §§VI.B.1.b-d.

Nor did Alvotech's experts show that any motivation to increase above 2 mg would lead specifically to 8 mg, rather than to a lower dose—*e.g.*, 3 mg in 75 μ L or 5 mg in 100 μ L—that preserved the established 40 mg/ml or 50 mg/ml concentrations. Ex.2051, ¶¶101, 144; Ex.2052, ¶¶165-171. The selection of 8 mg reflects hindsight, not prior-art motivation. Vitti confirms the point: its treatment-burden solution was VEGF/Ang-2 combination therapy, using 40 mg/ml aflibercept and potentially increasing the anti-Ang-2 antibody concentration, not escalating aflibercept dose or concentration. Ex.1007, ¶¶15, 198-201, 238, 260-70; Ex.2051, ¶¶123-124, 153, 159; Ex.2052, ¶¶172-73; *infra* §VI.B.1.b.

The admissions from Alvotech's experts underscore these defects. Dr. Falconer acknowledged that high-concentration formulations present high-viscosity and aggregation challenges, Ex.2046, 85:15-85:24; that selecting 114.3 mg/ml aflibercept would be riskier than selecting 100 mg/ml or below, Ex.2046, 206:13-

19; that (*contra* his declaration) Vitti does not teach stable aqueous aflibercept formulations at 114.3 mg/ml, Ex.2046, 73:14-17; and that a POSA would have “no idea” where they were in the viscosity-concentration curve for aflibercept at that concentration, Ex.2046, 106:11-108:2. Dr. D’Amico agreed that an overly viscous formulation would be “no good,” and declined to opine that a POSA would have used Larson’s viscosity-lowering dyes. Ex.2053, 296:1-19, 420:13-423:23, 425:19-426:7. As detailed below, the record does not merely lack a motivation to pursue an 8-mg intravitreal aflibercept dose; it affirmatively taught away from that dose. *Infra* §§VI.B.1.b-d.

ii. The POSA Had No Reasonable Expectation of Success of Treating with 8 mg

The POSA had no reasonable expectation of success in pursuing an 8 mg dose to treat eye disorders. Beyond intraocular pressure risks explicit in AU Label, *supra* §VI.B.1.a.i.2, the POSA recognized that inflammation was associated with higher doses of anti-VEGF agents. Ex.2052, ¶¶195-97. In one ranibizumab study, a higher concentration of 40 mg/ml (2 mg) led to “moderate to severe” inflammation, whereas four times less (0.5 mg) exhibited only “absent to moderate” inflammation. Ex.2014, 727-28. In another ranibizumab study, patients experienced dose-dependent inflammation and “dose-limiting toxicity.” Ex.2018, 1049-52. Genentech later revisited a 2-mg product without the same inflammation signals in

the HARBOR trial, but it failed to provide benefit over the lower dose. *Supra* §VI.B.1.a.i.3.

Multiple efforts to develop higher-dose anti-VEGF drugs failed due to inflammation-related side effects. FDA declined to approve abicipar, a 2.0-mg product with a higher molar concentration than aflibercept, due to high rates of intraocular inflammation. Ex.2008. Similarly, brolucizumab was associated with elevated intraocular inflammation, Ex.2024, 92; Ex.2012, leading to cases of “irreversible severe vision loss” and its abandonment by clinicians. Ex.2013.

Higher doses of anti-VEGF agents also were associated with increased cardiovascular events, especially in patients with underlying risk factors. Ex.2052, ¶¶198-199; Ex.1058 at 80. Intravenous aflibercept at 3 mg/kg resulted in dose-limiting hypertension and proteinuria in two of five patients. Ex.1026, 6. Other clinical studies involving anti-VEGF agents reported mixed results regarding increased incidence of strokes. While cardiovascular events were rare with intravitreal administration of 2 mg aflibercept, the POSA would have been concerned about serious safety issues at a much higher 8 mg dose. Ex.2052, ¶¶198-200.

b. The Claimed Concentrations Were Not Obvious.

Alvotech’s assertions regarding the claimed concentrations did not survive Dr. Falconer’s deposition. He acknowledged that each prong of Alvotech’s (and his

Declaration's) argument fails: Vitti and the other cited art did not disclose, or motivate the POSA to pursue, a stable intravitreal aflibercept formulation at 114.3 or 103-126 mg/ml; and the POSA lacked a reasonable expectation of success in doing so. Ex.2046, 39:10-14, 73:14-17, 75:5-7, 107:14-108:2, 132:6-12. When asked “[h]ow many formulations suitable for intravitreal administration containing at least 100 [mg/ml] of a VEGF-inhibiting fusion protein ... does Vitti disclose to the POSA[,]” Dr. Falconer replied: “None.” Ex.2046, 53:22-54:3; Ex.1007, ¶¶87, 94, 127, 198-201.

i. The POSA Was Not Motivated To Formulate Aflibercept at High Concentrations

1. The Prior Art Taught Against Increasing Concentration

Alvotech argues that a “POSA would have been motivated to treat angiogenic eye disorders with high-concentration VEGF antagonist.” Pet.19-20. Not so. The prior art taught that high-concentration formulations—especially intravitreal formulations—were plagued with instability and viscosity issues. Ex.2051, ¶¶103-105. Protein aggregation, one example of instability, can trigger “an immune response” that “could result in vision loss.” *Mylan*, 738; Ex.2051, ¶¶79-85. These stability concerns are exacerbated with synthetic proteins like aflibercept, which “lack the evolutionary optimization for stability” of naturally-occurring antibodies. Ex.2051, ¶¶104; *Mylan*, 744-45.

Viscosity is also a critical concern for intravitreal formulations. High viscosity can cause the needle or eye to move around or the needle to pop off the syringe during injection. Ex.2052, ¶¶66-68; *infra* §VI.B.1.d. A POSA would know that viscosity increases exponentially with concentration, but, as Dr. Falconer agreed, the exponential concentration/viscosity curve for aflibercept was unknown before the invention. Ex.2046, 107:14-23; Ex.2051, ¶¶90-95, 128-129. Thus, a POSA would have been discouraged from more than doubling Vitti's 40-mg/ml examples (and Eylea) to reach the claimed concentrations, given the risk of dramatically increasing viscosity. Ex.2051, ¶¶126-130.

The POSA investigating high-concentration, lower-injection-frequency VEGF antagonist formulations would have discovered a trail of failed projects and cautionary tales. As of 2018, sophisticated pharmaceutical companies were attempting (or had attempted) to develop intravitreal formulations dosed with less frequency—brolucizumab (120 mg/ml VEGF antagonist), higher-concentration ranibizumab (at 4x higher concentration than the highest-concentration marketed formulation), and abicipar. Abicipar failed to obtain FDA approval, and clinical trials for brolucizumab and higher-concentration ranibizumab were terminated, all because of unacceptable intraocular inflammation. Ex.2051, ¶¶106-110; Ex.2052, ¶¶134-37. Squarely contrary to the factual premise of both Alvotech's (Pet.44) and his declaration's motivation argument (Ex.1004, ¶¶172-73), Dr. Falconer conceded

that, in fact, there was no “trend [toward high concentration] that the POSA associated with intravitreal formulations as of 2018.” Ex.2046, 132:6-12; Ex.2051, ¶¶111-113. Despite the efforts of numerous companies, there were no high-concentration intravitreal formulations on the market in 2018. Ex.2051, ¶112; Ex.1045, 263-67.

2. Vitti Supplies No High-Concentration Motivation

Ignoring (improperly) the prior art as a whole, Alvotech cites Vitti for a motivation to pursue high-concentration aflibercept. But Vitti discloses stability only for 40-mg/ml aflibercept intravitreal formulations, Ex.2051 ¶¶62, 119, 122; Ex.1007, ¶¶197-217, 230-308—consistent with the art’s consistent disclosure of stable intravitreal aflibercept formulations only at 40 or 50 mg/ml. Ex.2051, ¶¶100-101. Given the severe stability and viscosity concerns and the failure of other higher-concentration formulations, a POSA would be discouraged from more than doubling the working prior-art concentrations to 114.3 or 103-126 mg/ml. Not even Vitti does so. Its treatment-burden solution was VEGF/Ang-2 combination therapy: its examples increased the anti-Ang-2 antibody concentration while keeping aflibercept at 40 mg/ml. Ex.1007, (57), ¶¶15, 198-201; Ex.2051, ¶¶123-124; Ex.2052, ¶172. Vitti therefore points away from escalating aflibercept concentration.

Ignoring Vitti’s examples, Alvotech resorts to three disparate paragraphs disclosing a broad genus of “VEGF antagonists” to argue that Vitti teaches “stable

aqueous pharmaceutical formulations for intravitreal injection containing up to 115 mg/mL of aflibercept” that render the claimed concentrations *prima facie* obvious. Pet.44, 47 (citing Ex.1007, ¶¶94, 108, 127). That premise is demonstrably false, which is why Alvotech’s expert abandoned the argument altogether and agreed that “Vitti doesn’t teach that aqueous formulations of aflibercept at 114.3 [mg/ml]” and “about 103 to 126 [mg/ml] ... would be stable.” Ex.2046, 73:14-21; Ex.2046, 75:5-7. Lest any doubt remain, he agreed that Vitti nowhere disclosed that “aqueous formulations of aflibercept at greater than 100 [mg/ml] are stable.” Ex.2046, 73:10-13.

Those admissions were no mistake—they reflect Vitti’s actual disclosure. Alvotech’s third cited Vitti paragraph discloses a “liquid formulation comprising of from 10 mg/mL to 120 mg/mL of anti-Ang-2 antibody and from 10 mg/mL to 100 mg/mL of aflibercept” “administered intravitreally in a volume of approximately upto 500 μ L”—which is clearly unsafe for intravitreal use. Ex.1007, ¶127; Ex.2052, ¶¶204-14. That passage does not disclose stable formulations throughout the range, and, in any event, the range ends at 100 mg/ml, below the claimed 114.3 or 103-126 mg/ml. The second paragraph simply defines what it means for “antibodies” to be “stable,” Ex.1007, ¶108; it does not apply to the fusion protein aflibercept. Ex.2051, ¶121; Ex.2046, 73:6-13 (agreeing that ¶108 is “about antibody stability” and “Vitti doesn’t teach that aqueous formulations of aflibercept at greater than 100 mgs per

ml are stable”); *contra* Ex.1004, ¶¶117, 172, 177, 184 (citing ¶108 to argue that Vitti’s aflibercept formulations “typically exhibit high levels of stability”)

Alvotect’s first cited Vitti paragraph fares no better. It states: “In certain embodiments, the pharmaceutical formulations are liquid formulations that may contain 5 ± 0.75 mg/mL to 100 ± 15 mg/mL of a VEGF antagonist.” Ex.1007, ¶94. This paragraph does not teach or suggest high-concentration aflibercept intravitreal formulations. Ex.2051, ¶¶115-119, 145-161. To start, it is silent as to routes of administration, which Vitti discloses include “intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes,” plus “eye drops, subconjunctival injection, subconjunctival implant, intravitreal injection, intravitreal implant, sub-Tenon’s injection or sub-Tenon’s implant.” Ex.1007, ¶¶114-119, 148-149. Each route presents different formulation constraints; therefore, the POSA would not understand the entirety of that concentration range as suitable for the specifically challenging intravitreal formulations. Ex.2051, ¶¶118-119, 148-149. Next, this paragraph says nothing about stability, nor conveys whether formulations at the higher end of that concentration range are sufficiently stable for intravitreal use. Ex.1007, ¶94; Ex.2046, 38:1-39:14, 73:14-17; Ex.2051, ¶¶121-122, 147, 151-154. Moreover, the disclosed range applies to “liquid formulations” containing “a VEGF antagonist”—a massive genus comprising “anti-VEGF antibodies,” small-molecule VEGF

inhibitors, “VEGF receptor-based chimeric molecules,” and other “VEGF-inhibiting fusion proteins.” Ex.1007, ¶85; Ex.2051, ¶¶116-117, 146; Ex.2046, 44:23-45:14, 48:23-49:2. Given the diversity among “VEGF antagonists”—*e.g.*, sunitinib, sorafenib, and pazopanib are among Vitti’s VEGF antagonists but cannot be formulated anywhere close to 100 mg/ml—and the formulation-related challenges posed by fusion proteins, the POSA would not understand a concentration range generally applicable to “VEGF antagonists” as applicable to every VEGF antagonists, much less fusion proteins like aflibercept. Ex.2051, ¶¶116-117, 146-147; Ex.2052 ¶¶167-68. Finally, the range is extremely broad, encompassing concentrations as low as 7.5 and as high as 115 mg/ml, including concentrations known as safe (*e.g.*, 10 mg/ml ranibizumab) and unsafe (*e.g.*, 40 mg/ml ranibizumab) for intravitreal administration, underscoring that the entire range was not appropriate for all VEGF antagonists. Ex.2051, ¶115, 150-154.

This concentration range did not teach or suggest stable 114.3 or 103-126 mg/ml aflibercept intravitreal formulations, as both experts now agree. Ex.2051, ¶¶150-161, 178; Ex.2046, 73:10-21. Likewise, Vitti’s disclosure of liquid formulations for numerous possible administration routes and a vast genus of molecules across an incredibly wide concentration range cannot trigger a presumption of obviousness for the narrow, claimed concentrations—114.3 and 103-126 mg/ml aflibercept for intravitreal use. *Janssen*, 141 F.4th at 1376; *Allergan*, 796

F.3d at 1305. Simply put, Alvotech “has failed to make th[e] threshold showing” that Vitti “teach[es] or suggest[s] a range for [aflibercept intravitreal formulations] that overlaps with the claimed range.” *ModernaTx*, 18 F.4th at 1373-74. And as explained above, the prior art taught away from pursuing high-concentration aflibercept intravitreal formulations, further precluding application of the presumption. *Allergan*, 796 F.3d at 1305; *DePuy*, 567 F.3d at 1326-27.

Even assuming Alvotech’s (false and expert-abandoned) premise that Vitti discloses stable aflibercept intravitreal formulations with concentrations ranging up to 115 mg/ml, Pet.21, 23-24, 32, 40, 43-44, 47, the POSA still would not have arrived at 114.3 or 103-126 mg/ml. That is because Vitti’s broadest range is “ 5 ± 0.75 mg/mL to 150 ± 22.5 mg/mL”—which reaches 172.5 mg/ml—not “ 5 ± 0.75 mg/mL to 100 ± 15 mg/mL”—which reaches 115 mg/ml. Ex.1007, ¶87; Ex.2046, 60:11-22, 105:16-19, 146:9-22. A POSA seeking (per Alvotech) to deliver 8 mg and believing (again, per Alvotech) that Vitti suggests desirable, stable, intravitreal aflibercept formulations up to 172.5 mg/ml would administer the 8 mg dose at the preferred injection volume—50 μ L—for a concentration of 160 mg/ml. Ex.1003, ¶358; Ex.2051, ¶¶155-157; Ex.2046, 147:25-148:9, 150:1-151:16; Ex.2053, 361:6-362:19. The POSA interpreting Vitti as Alvotech urged thus would have used 160—not 114.3 or 103-126—mg/ml to preserve the desired volume. Ex.2051, ¶¶155-157; Ex.2046, 147:8-148:9; Ex.2053, 190:8-191:25.

Alvotech and Dr. Falconer’s declaration resist this logical conclusion of their reasoning and assert with hindsight bias that the POSA would not use a concentration within Vitti’s ranges but above 115 mg/ml. Pet.71-72, Ex.1004, ¶251. But again, Dr. Falconer disavowed his declaration on cross-examination, agreeing that, “because it’s not true that 115 [mg/ml] is the upper limit disclosed in Vitti, the basis for [h]is [declaration’s] statement about the POSA’s motivation”—*i.e.*, “a POSA would not have been motivated to go above 115 mg/ml”—“is incorrect.” Ex.2046, 141:13-142:23. Drs. Falconer and Trout agree that Vitti provides no basis to conclude that a formulation with 100 ± 15.0 mg/ml, but not 150 ± 22.5 mg/ml, would have suitable stability and viscosity for intravitreal injection. Ex.2046, 150:1-151:16; Ex.2051, ¶¶155-157. As a result, even were Alvotech’s tortured reading of Vitti credited, Alvotech still cannot prove the POSA would be motivated to use 114.3 or 103-126 mg/ml aflibercept.

Finally, at Dr. Falconer’s deposition, Alvotech attempted to salvage its obviousness theory by shifting to Vitti’s disclosure in paragraph 94 of “about 100 mg/ml of a VEGF antagonist such as aflibercept” and characterizing claim 31’s 114.3 mg/ml concentration as a “routine optimization” of that disclosure. Ex.1007, ¶94; Ex.2046, 230:1-10. Not so. This theory—appearing nowhere in the Petition—fails on its own terms, as it requires the POSA to modify Vitti’s 100 mg/ml disclosure to achieve claim 31’s even higher concentration. But the POSA

categorically would not do so, given the known aggregation and viscosity risks of high-concentration protein formulations. *Supra* pp.30-33. First, Dr. Falconer admits that “[b]ecause the POSA doesn’t have an understanding from Vitti that aflibercept would be stable, the POSA wouldn’t have a reasonable expectation of success in achieving formulations of aflibercept that would be suitable for intravitreal administration[.]” Ex.2046, 74:17-24. Second, the POSA would not consider a 15% aflibercept concentration increase (from Vitti’s 100 mg/ml with unknown viscosity, Ex.2046, 73:22-74:8, 107:14-108:2, to claim 31’s 114.3 mg/ml) to be “minor,” *contra* Ex.1004, ¶¶244-246, because absent knowledge of the aflibercept concentration-viscosity curve (which Dr. Falconer conceded was unavailable), the POSA would not know whether that increase occurs in a relatively flat or very steep portion of the curve. Ex.2051, ¶¶128-130, 138, 154; Ex.2046, 106:8-10, 106:15-107:10, 107:20-108:2, 108:18-21. The POSA could not predict whether that increase would result in problematic viscosity-, stability-, or aggregation-related issues. Ex.2051, ¶¶128-130, 138, 154. As Dr. Falconer conceded, such an increase “would be a riskier decision for the skilled formulator,” and that he did not know what a 15% increase in concentration would do to aggregation, stability, or viscosity. Ex.2046, 72:16-75:7, 85:15-86:24, 107:14-108:2, 205:10-206:19; Ex.1004, ¶251. Accordingly, the POSA would not believe that increasing concentration would confer benefits (*e.g.*, greater durability) while avoiding significant downsides (*e.g.*,

higher viscosity and instability) and thus would not further increase the concentration beyond the 100 mg/ml Vitti discloses. *See, e.g., Pfizer v. Apotex*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (optimization flows from desire to “improve upon what is already generally known”); *Endo Pharm v. Actavis*, 922 F.3d 1365, 1376 (Fed. Cir. 2019); *Honeywell v. Mexichem Amanco Holding*, 865 F.3d 1348, 1356 (Fed. Cir. 2017) (“[R]easoning that one would no more have expected failure than success is not a valid ground for holding an invention to have been obvious.”). The POSA would have no motivation to optimize toward formulations with lower stability or increased viscosity, especially given Vitti’s alternative co-administration approach.

ii. The POSA Would Not Have a Reasonable Expectation of Success in Using the Claimed Concentrations

Alvotech cannot prove a reasonable expectation of success in achieving an intravitreal formulation with 114.3 or 103-126 mg/ml aflibercept. Dr. Falconer admitted as much. Ex.2046, 55:21-56:3 (“Q. The POSA would not have a reasonable expectation of success based upon Vitti in achieving aqueous formulations suitable for intravitreal administration containing at least 100 mgs per ml of a VEGF-inhibiting fusion protein falling within the scope of Vitti’s VEGF antagonist definition, correct? A. That’s correct because the definition is so broad. Yes.”). Vitti’s “VEGF antagonists” definition encompasses a massive genus of

protein structures. Ex.2051, ¶¶116-117. Their properties vary with their structures, making critical formulation parameters such as stability and viscosity unpredictable without any experimental data. Ex.2051, ¶¶133-135; Ex.2046, 72:16-19. Within this broad genus, stability and viscosity concerns are magnified with fusion proteins like aflibercept. Ex.2051, ¶138; *Mylan*, 737, 742, 744-45. As Dr. Falconer testified, “the practicing formulation scientist” would understand that a “60 percent increase in concentration will have a serious effect on the viscosity,” Ex.2046, 148:25-149:6; moving from the prior-art exemplary aflibercept intravitreal formulations at 40 and 50 mg/ml to 114 mg/ml is a far larger jump. Indeed, because the exponential concentration/viscosity curve for aflibercept was unknown, the POSA could not have expected smaller concentration increases (such as 100-114.3 mg/ml) to produce acceptable viscosities. Ex.2051, ¶¶135-138, 176. A POSA would not reasonably expect to take a protein with known stability and viscosity concerns, more than double its concentration from what worked in the prior art, and obtain the claimed formulations suitable for intravitreal use. Dr. Falconer agreed: “Because the POSA doesn’t have an understanding from Vitti that aflibercept would be stable, the POSA wouldn’t have a reasonable expectation of success in achieving formulations of aflibercept that would be suitable for intravitreal administration.” Ex.2046, 74:17-24.

c. The POSA Would Choose an Injection Volume of 50 μ L, not 70 μ L.

A POSA had neither a motivation to use a 70- μ L volume nor a reasonable expectation of success in achieving that volume. Alvotech relies on Vitti's volumes of "up to 100 μ L." Pet.44; Ex.1007, ¶127. But that wide range does not render the specific 70- μ L volume *prima facie* obvious. *Janssen*, 141 F.4th at 1376.

The POSA had no motivation to select 70 μ L over the preferred 50 μ L. Clinicians strongly preferred 50 μ L because higher volumes increased risks of intraocular pressure spikes. *Supra* §VI.B.1.a.2 (AU Label warning that overdosing "associated with increased injection volume and subsequently with increased intraocular pressure"); Ex.2052, ¶¶69-74; 204-214; Ex.2053, 190:8-191:25. Dr. D'Amico confirmed that a clinician would "prefer to deliver the 8mg dose of aflibercept in the same 50 μ L volume, or a volume as close to 50 μ L as possible." Ex.1003, ¶359; Ex.2053, 300:11-21. Dr. Falconer admitted that the POSA was "unaware of any disclosure of a 70-microliter injection volume for intravitreal administration" and that Dr. D'Amico did not tell him "that the POSA would select an injection volume of 70 microliters." Ex.2046, 151:25-152:8. Even accepting Alvotech's discredited premises that the POSA would use 8 mg aflibercept and the "high end" of Vitti's concentration disclosures, the POSA would have selected 160 mg/ml in the preferred 50- μ L volume—not 70 μ L. *Supra* §VI.B.1.b.1; Ex.2046, 147:3-148:9.

Alvotech’s argument that the POSA would reach 70 μ L by “routine optimization” is transparent hindsight. Pet.44-45. A POSA would not have “routinely optimized” toward 70 μ L when doing so worsened—not improved—patient outcomes by increasing intraocular pressure risk. Ex.2053, 190:15-191:20; Ex.2052, ¶¶204-212; *Pfizer*, 480 F.3d at 1368.

d. Alvotech’s Viscosity Theory Lacks Aflibercept Data and Misuses Larson.

All agree that viscosity increases exponentially with protein concentration and that high viscosity renders intravitreal formulations unsuitable. Ex.2051, ¶¶90-96; Ex.2052, ¶¶66-68; 215-220; Ex.1004, ¶¶48-50; Ex.2046, 67:8-68:4, 106:8-10; Ex.1003, ¶¶182, 277-278; Ex.2053, 222:2-18, 296:1-19, 420:13-423:23. Viscosity increases shear stress through the narrow-bore needle, promoting protein aggregation and particulate formation—especially serious concerns for intravitreal injection. Ex.2051, ¶¶79, 93, 105; Ex.2016, 3, 20-21. As Dr. D’Amico explained, a clinician needs an intravitreal formulation with appropriate viscosity to pass through a 30-gauge needle; if the formulator “makes tar,” it is “no good.” Ex.2053, 296:1-19. Dr. Bressler agrees—viscosity affects intravitreal administration, and the POSA would not deviate from the typical 30-gauge needle. Ex.2052, ¶¶215-220.

Yet Alvotech has no prior-art viscosity evidence for high-concentration aflibercept formulations. Dr. Falconer admitted the POSA had no knowledge of an aflibercept concentration-viscosity curve and “would have no idea where they are

on that curve for aflibercept based on information in the prior art.” Ex.2046, 107:14-108:2. He agreed “there’s no data in the prior art about the viscosity of aflibercept formulations,” Ex.2046, 103:25-104:4, and the POSA “would not have any data to draw upon indicating the viscosity of an aflibercept formulation at over 100 mgs per ml,” Ex.2046, 201:5-9. Those admissions foreclose Alvotech’s contention (Pet.34-35, 47-48) that a POSA could predict that increasing aflibercept concentration to the claimed levels would yield the claimed viscosity.

Alvotech misreads Larson. Larson generically references formulations having a viscosity “less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25°C.” Pet.32-35, 47-48; Ex.1010, ¶¶75, 77. Dr. Falconer asserts, based on that disclosure, that the POSA could reasonably expect to arrive at the claimed viscosity. Ex.1004, ¶¶124, 127-128. But Larson is a general protein-formulation reference about reducing viscosity with water-soluble organic dyes, not formulating aflibercept for intravitreal injection. Ex.1010, Abstract, ¶¶23, 74-77; Ex.2051, ¶¶65, 127-130, 136. Ex.2052, ¶¶221-229. Larson discloses viscosity for subcutaneous and intramuscular, not intravitreal, injections, Ex.1010, ¶224; Ex.2051, ¶136, and Dr. Falconer admitted that Larson discloses no viscosity values for intravitreal administration. Ex.2046, 116:18-22, 118:10-119:2. A POSA would not inject Larson’s dyes into the eye absent evidence of intravitreal compatibility, and the prior art shows that chronic intravitreal exposure to dyes is toxic. Ex.2052,

¶¶226-229; Ex.2051, ¶136; *Mylan*, 725-26, 739 (“toxicity of [the] proposed combination” is highly relevant to obviousness). Dr. D’Amico offered no opinion that a POSA would use Larson’s viscosity-lowering dyes intravitreally. Ex.2053, 425:19-426:7.

None of Alvotech’s references supplies the missing viscosity evidence. Dr. Falconer conceded: “[t]here’s no viscosity data in any of” Vitti, Dix, Furfine, and Fiedler. Ex.2046, 109:22-110:7. He also admitted that Fiedler “doesn’t teach the POSA anything about the viscosity of an aflibercept formulation at any particular concentration,” Ex.2046, 82:18-83:5, and Furfine provides “no viscosity data for a formulation ... of at least 100 mgs per ml of aflibercept,” Ex.2046, 200:3-6. Dr. D’Amico deferred to Dr. Falconer on viscosity, which was outside his expertise. Ex.2053, 222:2-17, 423:13-16.

Even if considered, Larson provides no reasonable expectation of success for aflibercept. Larson mentions Eylea only in a laundry list of biological products, Ex.1010, ¶¶137-190, and its viscosity data are not for aflibercept or any VEGF receptor fusion protein, Ex.1010, ¶258; Ex.2051, ¶¶65, 127-129, 136-138; Ex.2052, ¶¶ 224-225. Larson teaches that, “in the absence of a viscosity-lowering water soluble dye” (which neither Alvotech expert asserts the POSA would use), high-concentration protein formulations “may have viscosities greater than 100 cP ... or even greater than 1,000 cP”—well outside the claimed range. Ex.1010, ¶75.

Viscosity at high concentration is protein-specific: it depends on, *inter alia*, each protein's surface charge distribution and hydrophobic patches, and strategies that reduce viscosity for one protein may fail for another. Ex.2051, ¶¶90-96, 129, 138. Larson's data show very different viscosity behavior across different antibody formulations, with every formulation having a viscosity far above the claimed 5-15 cP range. Ex.1010, ¶258; Ex.2051, ¶¶65, 127. A POSA could not infer from Larson's antibody and dye data that high-concentration aflibercept formulations would have viscosities of about 5-15 cP.

Nor can Alvotech invoke the overlapping-range presumption. Larson's ranges are not disclosed for intravitreal aflibercept formulations; they are viscosity goals for dye-containing formulations used outside the intravitreal context. The claimed formulations differ from Larson in the protein identity, route of administration, dose, concentration, volume, and viscosity-reducer. Those differences foreclose a *prima facie* range case. *Janssen*, 141 F.4th at 1376.

Alvotech cannot avoid that evidentiary gap by resorting to "routine optimization." Pet.34-35, 63. Routine optimization presupposes a known starting point and a result-effective variable that the POSA adjusts with a reasonable expectation of success; it does not supply missing prior-art teachings or substitute for aflibercept-specific viscosity data. *Pfizer*, 480 F.3d at 1368; *Endo*, 922 F.3d at 1376. Routine optimization would point in the opposite direction: because protein

concentration drives viscosity, a POSA seeking to reduce viscosity would reduce concentration, not increase it as claimed. Ex.1004, ¶50; Ex.2046, 106:8-10; Ex.2001, 295-96. Lowering concentration, however, would require increasing volume, confirming that the claimed formulation required balancing interrelated dose, volume, concentration, and viscosity constraints—not routine adjustment of a single variable. Ex.2001, 295-96.

These facts separately defeat motivation and expectation of success. On motivation, a POSA seeking an intravitreal aflibercept product would understand that increasing concentration increases viscosity, that intravitreal administration imposes unusually stringent viscosity constraints, and that Larson's dye-based approach is unsuitable for intravitreal injection. Ex.2051, ¶¶90-96, 126-130, 170; Ex.2052, ¶¶66-68; 215-229; Ex.2053, 296:1-19, 420:13-423:23. On reasonable expectation of success, the art did not disclose the aflibercept data required to expect that the claimed high-concentration formulations would achieve the claimed viscosity. Ex.2051, ¶¶135-138, 176; Ex.2046, 107:14-108:2, 148:17-22. Alvotech's theory thus selects Larson for viscosity targets that were not taught for intravitreal aflibercept while ignoring both Larson's dye-dependent solution and the absence of prior-art concentration-viscosity data for aflibercept. That argument fails miserably.

2. Claims 1 and 4-30

Claims 1 and 4-30 were not obvious for largely the same reasons as claims 31-38. The POSA lacked any motivation to use an 8 mg or higher dose of a VEGF receptor fusion protein or any reasonable expectation of successfully using such a dose. *Supra* §VI.B.1.a; Ex.2052, ¶¶144-146; Ex.2051, ¶¶99-101. And for the reasons above, the POSA had no motivation or reasonable expectation of success to make a VEGF receptor fusion protein formulation with a concentration of at least 100 mg/ml. *Supra* §VI.B.1.b; Ex.2051, ¶¶90-138. Vitti's disclosures cannot establish a *prima facie* case of obviousness for the at least 100-mg/ml range recited by claim 1 for the same reasons as for claims 31-38. *Supra* §VI.B.1.b; Ex.2051, ¶¶90-138. The POSA would not reasonably expect success in fitting at least about 8 mg into a volume of less than 100 µL. *Supra* §VI.B.1.a-c; Ex.2051, ¶¶99-101, 132. And Larson would not motivate the POSA with a reasonable expectation of success to achieve high-concentration VEGF receptor fusion protein formulations with the claimed viscosities, nor does it render the claimed viscosity range *prima facie* obvious. *Supra* §VI.B.1.d; Ex.2051, ¶¶126-130, 135-138; Ex.2052, ¶¶66-68; 215-229. Claims 1-30 therefore were not obvious.

3. Objective Evidence Supports Nonobviousness

While Alvotech fails to show *prima facie* obviousness, objective evidence of teaching away, long-felt need, and failure of others further supports nonobviousness.

Dr. D'Amico had no opinion on whether others had tried and failed to make the claimed invention; lacked “the qualifications to understand” how others’ failures factor into the obviousness analysis; and did not know how commercial success bears on obviousness. Ex.2053, 214:13-217:10.

Objective evidence is especially important here because Dr. D'Amico's analysis confirms the risk of hindsight. He formed his motivation opinions based on information unavailable to the POSA, including “high dose Eylea,” the patent's disclosure, and “the work of those inventors,” and he testified that the inventors' disclosure made the claims more likely obvious. Ex.2053, 237:2-24.

First, in addition to refuting motivation, teaching away constitutes objective evidence of nonobviousness. *Polaris*, 882 F.3d at 1069. Prior art, including AU Label, discouraged the POSA from: (1) pursuing the claimed 8 mg aflibercept dose, (2) pursuing high-concentration aflibercept (including because of viscosity concerns), and (3) increasing injection volume by 40%. *Supra* §§VI.B.1.a-d; Ex.2051, ¶¶180-181; Ex.2052, ¶¶153-164; 195-202; 166-171. Dr. D'Amico confirmed he would rather inject 50 µL than 60 or 100 µL, and that lower volumes reduce the risk of dangerous intraocular-pressure spikes. Ex.2053, 190:8-191:25. He likewise testified that “high volumes” and “[h]igh viscosities are bad,” and that 30-gauge needles require an appropriate volume and viscosity. Ex.2053, 294:15-296:19.

Second, as here, “[e]vidence of long-felt need is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand.” *Millenium*, 862 F.3d at 1369. There was a long-felt, “unmet need for a long-acting anti-VEGF that decreases the treatment burden for patients with nAMD,” Ex.2022, 1036, along with a failure of others to meet that need. Ex.2051, ¶182; Ex.2052, ¶¶63-64, 134-137. Alvotech agreed it was “long known to minimize [intravitreal] injections in the care of patients,” Pet.1, as did Dr. D’Amico. Ex.2053, 163:15-164:5, 171:7-12. Multiple companies failed to develop VEGF-antagonist products to meet that need. *Supra* §II.B; Ex.2051, ¶¶183-184; Ex.2052, ¶¶134-137. Despite abicipar’s “high molar dose,” Ex.2022, 1028, it was abandoned “because it caused inflammation.” Ex.2053, 164:12-167:3; Ex.2008; *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 460 F. Supp. 2d 659, 662 (D.N.J. 2006) (“not getting to market with FDA approval is an appropriate benchmark for failure [of others]”). Brolucizumab was developed to lessen treatment burden and contained a higher (6 mg) dose than Eylea (2 mg), yet resulted in inflammation, Ex.2024, 92; Ex.2012, “irreversible severe vision loss” and abandonment by ophthalmologists, Ex.2013; Ex.2053, 188:9-189:8. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Ex.2125, 14; Ex.2126, 22 (“Higher molar doses of anti-VEGF do not lead to greater efficacy or durability.”).

Despite that skepticism, Regeneron’s inventors succeeded. The claimed composition, marketed as Eylea HD, uses a higher dose than any anti-VEGF intravitreal product. Ex.2007, 1; Ex.1001, Example 13, Figs. 19A-19E (stability data); *id.*, Examples 3, 5, 9, Figs. 3A-3C, 5, 9 (viscosity data); Ex.2052, ¶¶138-142, 184-185; Ex.2053, 187:23-188:5, 189:10-13. Unlike abicipar and brolucizumab, Eylea HD achieved the same efficacy as Eylea “despite the longer treatment intervals of every 12 or 16 weeks, which allowed for fewer total injections,” and “[j]ust as important...the rate of adverse reactions in the 8-mg aflibercept group was infrequent and consistent with the known rate for the 2-mg aflibercept.” Ex.2025, 5; Ex.2007, 1; Ex.2052, ¶¶141-142.⁴ The inventors’ success in achieving extended dosing with efficacy and safety, where others failed, strongly supports nonobviousness. Ex.2051 ¶¶183-184; *Millenium*, 862 F.3d at 1369; *Amgen*, 66 F.4th at 964 (crediting long-felt need and failure of others where “many PDE4 inhibitors

⁴ Vabysmo (faricimab) successfully extends dosing using Vitti’s approach of inhibiting both VEGF and Ang-2, Ex.2026, and uses a lower dose (6 mg) than the claimed 8 mg.

failed to progress in experimentation and trials or were not sufficiently effective at tolerable doses”).

C. Ground 2: Alvotech Cannot Prove Obviousness over Furfine, Dix, AU Label, Fiedler, and Larson

1. Claims 31-38

Ground 2 asserts that claims 31-38 are obvious over Furfine, Dix, AU Label, Fiedler, and Larson. Pet.67-75. Ground 2 recycles arguments from Ground 1 and fails for many of the same reasons. *Supra* §VI.B.1. Swapping Furfine, Dix, and Fiedler for Vitti does not cure Ground 1’s shortcomings—none discloses any aflibercept concentration above 100 mg/ml, much less 114.3 or 103-126 mg/ml.

a. Alvotech’s Recycled Ground 1 Arguments Fail

Motivation. Alvotech again contends (Pet.49) that the POSA was motivated to increase dose and concentration, in hopes of increasing treatment duration. Alvotech is wrong. *Supra* §§VI.B.1.a.i-VI.B.1.b.i. To the extent Alvotech relies (Pet.49-53) on the same references as Ground 1 to show safety and efficacy of high-dose formulations, those references do not support the claimed 8 mg dose at 100+ mg/ml. *Supra* §VI.B.1.a.i; Ex.2051, ¶¶216-226; Ex.2052 ¶¶143-203.

Teaching Away. As in Ground 1, the art as a whole—including AU Label’s characterization of 8 mg as an “overdose”—motivated against and taught away from high-dose, high-concentration formulations. *Supra* §VI.B.1; Ex.2051, ¶¶194, 213; Ex.2052 ¶¶153-164; 195-202.

Reasonable Expectation of Success. Alvotech’s repetition of its Ground 1 theories (Pet.53-55) still fails, *supra* §VI.B.1.a.ii-VI.B.1.d, and reliance (Pet.54-55) on Dix, Furfine and Fiedler do not plug the holes, as they disclose no viscosity data, Ex.2046, 149:7-10; Ex.2051, ¶¶227-233.

Alvotech rehashes its argument the POSA would use 70 µL to administer 114.3 mg/ml with an 8 mg dose. Pet.68-73. But as explained above (§VI.B.1.c) and below, a POSA had no motivation to achieve a concentration of 114.3 or 103-126 mg/ml.

b. Furfine, Dix, and Fiedler Did Not Motivate the POSA To Use Concentrations Above 100 mg/ml Intravitreally With a Reasonable Expectation of Success.

In Ground 2, for the concentration limitations, Alvotech substitutes Furfine, Dix, and Fiedler for Vitti. Pet.68-73. That substitution leads *further* from the claims: Furfine discloses formulations with 1-100 mg/ml concentrations (examples limited to 50 mg/ml or less), Ex.1005, 24-9, 7:60-10:49; Dix discloses non-intravitreal liquid 50-100 mg/ml VEGF trap formulations , Ex.1006, 2:20-34, 9:20-10:55; and Fiedler discloses 1-100 mg/ml VEGF antagonist concentrations , Ex.1011, ¶76. None disclose any aflibercept formulation above 100 mg/ml, much less the concentrations of claims 31-38. Alvotech therefore cannot (and does not) invoke any “overlapping ranges” presumption. *E.I. DuPont v. Synvina*, 904 F.3d 996, 1006 (Fed. Cir. 2018). Because the claimed [range does not overlap with a prior art range, the challenger

must show “reason to attempt to get within the claimed range, as is required to make such an obviousness finding.” *Chemours Co. FC, LLC v. Daikin Indus.*, 4 F.4th 1370, 1377 (Fed. Cir. 2021).

Attempting to gap-fill, Alvotech handwaves “routine optimization” to increase from 100 mg/ml to 114.3 mg/ml, because this represents “less than a 15% difference.” Pet.68-70; Ex.1004, ¶¶244-45. But this conclusory assertion ignores the well-known stability and viscosity challenges and dangers (including blindness) of high-concentration protein formulations that are especially pronounced for intravitreal fusion-protein formulations. *Supra* §VI.B.1.b.i.1. The experts agree that the prior art disclosed no examples of 100 mg/ml aflibercept intravitreal formulations, so the viscosity or stability of such formulations was unknown. Ex.2051, ¶220; Ex.2046, 77:4-81:12, 82:9-83:4, 149:7-10. Even assuming (incorrectly, *supra* §VI.B.1.b.i.1) the POSA began at 100 mg/ml, there was no motivation—from Alvotech’s references or otherwise—to increase the concentration further, much less to the specific claimed values (114.3, 103-126 mg/ml). Ex.2051, ¶¶192-207, 220-224. And increasing to 114.3 mg/ml was anything but routine. All agree that viscosity increases exponentially with concentration, meaning even small increases in the high-concentration region can affect viscosity dramatically, and no prior-art data showed whether aflibercept at 114.3 or 103-126 mg/ml would have acceptable viscosity for intravitreal

administration. Ex.2051, ¶¶208, 214-215, 226, 232-233; Ex.2046, 105:20-107:23. A 15% change at one point in a curve may slightly increase viscosity, while a 15% change at a different point may double (or more) viscosity. Ex.2051, ¶221; Ex.1001, Fig.5 (15% concentration increase at 140 mg/ml roughly doubles viscosity). Dr. Falconer agreed that the POSA had no knowledge of the concentration/viscosity curve for aflibercept, Ex.2046, 107:14-108:2, so there was no basis to believe that increasing from 100 mg/ml (with no viscosity data, Ex.2046, 149:7-10) to 114.3 mg/ml would result in a suitable intravitreal formulation. Ex.2051, ¶¶220-222, 232-233; *supra* §VI.B.1.b.ii.

Alvotech argues (Pet.54-55) that Dix, Furfine, and Larson assuaged any viscosity concerns. As explained above, this argument fails. *Supra* §VI.C.1.a; Ex.2051, ¶¶226, 232-233. In brief: Dix discloses no viscosity data and is directed to non-intravitreal formulations; Furfine likewise discloses no viscosity data and its examples reach only 50 mg/ml; and Larson's viscosity teachings are directed to subcutaneous and intramuscular formulations with dyes, not intravitreal use. *Supra* §VI.B.1.d; Ex.2046, 79:18-24. Due to these serious stability and viscosity concerns, a POSA would lack both a motivation and reasonable expectation of success in achieving intravitreal formulations with a 114.3 or 103-126 mg/ml concentration.

Alvotech and Dr. Falconer also rely on Vitti as "confirming that a 15% change in protein concentration is relatively minor." Pet.69; Ex.2046, 105:2-15. Vitti is not

a Ground 2 reference, so this reliance is improper. 37 C.F.R. §42.204(b)(4). Additionally, for the reasons explained in Ground 1, Vitti provides neither a motivation nor a reasonable expectation of success in using 114.3 or 103-126 mg/ml. Notably, Dr. Falconer disagreed with Alvotech's argument (Pet.71-72) that the POSA would use 114.3 mg/ml. Ex.2046, 142:18-23.

Alvotech finally argues that “a POSA would have been motivated to increase the concentration of the 100 mg/mL aflibercept formulations taught in Furfine, Dix, and Fiedler” according to the “movement in the field of anti-VEGF drugs toward higher-dose, higher-concentration formulations.” Pet.70 Drs. Trout and Falconer (at deposition) agree that this “movement in the field” did not apply to intravitreal formulations. Ex.2051 ¶¶103-114, 220-224; Ex.2046, 123:23-132:12.

2. Claims 1 and 4-30

Claims 1 and 4-30 were not obvious over Alvotech's Ground 2 references for many of the same reasons as claims 31-38. The POSA had no motivation to use, nor reasonably expected success in using, an 8 mg dose (or higher). *Supra* §VI.B.1.a; Ex.2051, ¶¶189-191; Ex.2052 ¶¶143-203.

Nor was it obvious to use a concentration of at least 100 mg/ml. *Supra* §VI.B.1.b; Ex.2051, ¶¶103-114. Nothing in Dix, Furfine, or Fiedler supports a contrary finding. Furfine and Fiedler's disclosed 1-100 mg/ml ranges, without any embodiments or stability or viscosity data for high-concentration formulations, did

not render obvious high-concentration formulations. Furfine’s examples use 50 mg/ml or less, while Fiedler focuses on lower concentrations of 10, 25, and 40 mg/ml—neither directed the POSA to the upper bound of their concentration ranges. Ex.1005, 7:60-10:47; Ex.1011, ¶68; Ex.2051, ¶¶192-195. Dix, meanwhile, discloses only subcutaneous and intravenous—not intravitreal—formulations; the POSA would understand both its 100 mg/ml liquid-formulation examples (which contain 20% sucrose and are thus hypertonic and high-viscosity) and 100 mg/ml lyophilized-and-reconstituted examples (which the POSA would understand are storage-stable when lyophilized, not when reconstituted) to be unsuitable for intravitreal use. Ex.2051, ¶¶196-207; Ex.2046, 80:22-81:8; Ex.1006, 2:20-35, 9:20-65, 10:5-11:34. And absent any examples or stability or viscosity data for the 100 mg/ml, 5% sucrose formulations recited by Dix claims 1-2, the POSA would not have been motivated with a reasonable expectation of success to inject such a formulation intravitreally, especially given Dix’s limited focus on subcutaneous and intravenous administration. Ex.2051, ¶¶196-207, 211-213.

Contra Alvotech (Pet.61), Dix, Furfine, and Fiedler do not support a *prima facie* obviousness case. To start, their disclosed ranges (50-100, 1-100, and 1-100 mg/ml, respectively) do not overlap with claim 1’s range (“at least 100 mg/ml.”). “High” protein concentration means 100 mg/ml or above, *e.g.*, Ex.2051, ¶95; Ex.2046, 91:10-17; Ex.2079, 1390, and the POSA would understand Dix, Furfine,

and Fiedler to disclose low-concentration ranges that do not overlap with claim 1's high-concentration range. *UCB*, 65 F.4th at 688 (“[T]he disclosure of a range is not a disclosure of the endpoints of the range or other discrete points within the range.”). Furthermore, any obviousness presumption is inapplicable because the prior-art ranges—encompassing numerous distinct concentrations—are very broad, Ex.2051, ¶¶192-207; *Allergan*, 796 F.3d at 1305, and concentration was not a result-effective variable, Ex.2051, ¶194; *Applied Materials*, 692 F.3d at 1295. Finally, the multiple differences between the Dix (100 mg/ml subcutaneous/intravenous formulation unsuitable for intravitreal administration) and Fiedler (1-100 mg of “VEGF antagonists” including antibodies) disclosures and claim 1 (at least 100 mg/ml of a VEGF receptor fusion protein for intravitreal administration) defeat any presumption of obviousness, as does the prior art teach-away from high concentrations. Ex.2051, ¶¶193, 196-207, 211-213; *supra* §VI.C.1.b.

Additionally, the POSA would not reasonably expect success in formulating 8 mg or more in a volume of less than 100 µL. Ex.2051, ¶¶190, 210.

Finally, Larson does not render the claimed viscosities obvious, and Dix, Furfine, and Fiedler disclose no viscosity data. *Supra* §§VI.B.1.d, VI.C.1.b; Ex.2051, ¶¶208, 214-215. Claims 1-30 therefore are patentable.

3. Objective Evidence Supports Nonobviousness

Objective evidence supports nonobviousness for the same reasons explained in Ground 1. *Supra* §VI.B.3.

D. Grounds 4-5: Alvotech Fails To Demonstrate Obviousness

In Grounds 4-5, Alvotech adds the Clinical Review (Ex.1008) to its combinations of Ground 1 references (Ground 4) and Ground 2 references (Ground 5). Pet.86, 88. Alvotech's arguments fail for all the reasons explained above with respect to Grounds 1 and 2. *Supra* §§VI.B-C. The Clinical Review provides no information about 8 mg aflibercept and thus cures none of the deficiencies of Grounds 1-2, nor does it provide support for the additional limitations in claims 2-3. Ex.1008, 8, 10; Ex.2052, ¶¶194, 230-231.

VII. Ground 3: Alvotech Has No Evidence That the Claims Lack Written Description

Ground 3 alleges lack written description. But Alvotech has nothing but legally insufficient attorney argument to support this theory: Its sole expert on the issue, Dr. Falconer, disavowed his written-description opinions and conceded that: (1) his declaration did not apply the correct legal standards, including because he failed to consider the POSA's knowledge, the originally filed claims, and materials incorporated by reference; (2) the claims have adequate written description; and (3) the patent's disclosures demonstrate the inventors' possession of the claimed formulations. Because "[m]ere attorney argument cannot carry Petitioner's burden,"

the Board should reject Alvotech’s written-description challenge. *Blackberry v. Zipit Wireless*, IPR2014-01509, 2016 WL 1244943, at *14 (P.T.A.B. Mar. 29, 2016); *Intuitive Surgical v. Ethicon*, IPR2018-01248, 2020 WL 594140, at *16 (P.T.A.B. Feb. 6, 2020).

A. Legal Standards

The written-description test “is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad*, 598 F.3d at 1351. The inquiry is “objective” and focuses on “the four corners of the specification from the perspective of a [POSA],” *id.*; thus, “a patentee may rely on information that is well-known in the art for purposes of meeting the written description requirement.” *Ajinomoto Co. v. ITC*, 932 F.3d 1342, 1359 (Fed. Cir. 2019); *Zoltek Corp. v. US*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (standard is “applied in the context of the state of knowledge at the time”). A “patent need not teach, and preferably omits, what is well known in the art.” *McRO v. Bandai Namco Games*, 959 F.3d 1091, 1102 (Fed. Cir. 2020).

The patent’s “[o]riginally filed claims have long been held to be part of the specification to be considered in any § 112 analysis.” *Allergan v. MSN*, 111 F.4th 1358, 1374 (Fed. Cir. 2024). Accordingly, if the originally filed claims recite an embodiment lacking a particular component, “that application disclose[s]

[embodiments] without [that component]” and thus provides written-description support for claims that do not recite that component. *Id.*

The analysis also may consider materials incorporated by reference into the specification. An entire reference may be incorporated when it is clear to the POSA “with sufficient particularity” that the patentee intended to incorporate the whole reference, as opposed to just a specific part. *Harari v. Lee*, 656 F.3d 1331, 1334 (Fed. Cir. 2011); *Paice v. Ford Motor*, 881 F.3d 894, 906-07 (Fed. Cir. 2018). Incorporated references “are effectively part of the host document as if they were explicitly contained therein.” *Arbutus Biopharma v. ModernaTX*, 65 F.4th 656, 662-63 (Fed. Cir. 2023). A U.S. patent incorporated by reference may provide written-description support. *Hayward Indus. v. Pentair Water Pool & Spa*, 721 F. App’x 974, 982 (Fed. Cir. 2018).

B. Dr. Falconer’s Deposition Testimony Is Fatal to Ground 3

Dr. Falconer’s declaration provided the sole evidence supporting Ground 3. He disavowed his opinions under oath, clearly and repeatedly, conceding that the claims are adequately described. His testimony categorically precludes finding the claims lack written description.

1. Dr. Falconer’s Declaration Did Not Apply the Correct Legal Standard

At the outset, Alvotech cannot prevail because Dr. Falconer—Alvotech’s sole expert opining on written description—acknowledged that he neither understood nor

applied the correct legal standards. To wit, he conceded that he “do[es]n’t understand the written description legal standard that [he] applied in rendering [his] written description opinions in this case.” Ex.2046, 156:9-23. He also failed to consider what was well known to the POSA—he “read the full text of the ’036 patent but [] didn’t also consider information that was not set forth in the ’036 patent including information that was well known to the POSA,” *id.*, 157:13-19, and wrongly “assum[ed]” that “something well known in the art needed to be described expressly in the ’036 patent in order to satisfy written description,” *id.*, 160:1-13.

Dr. Falconer also admitted that he never “analyze[d] the claims that were submitted by the inventors in their originally filed application,” and that he did not “believe” he had “seen those claims before.” *Id.*, 171:5-11. Indeed, he “ha[d]n’t seen [the file history] before,” and testified it “is erroneously listed among [his] list of materials considered in [his] declaration.” *Id.*, 172:25-173:8. Likewise, he “did not consider either of” two prior Regeneron patents incorporated by reference into the specification “in forming [his] opinion in this case,” *id.*, 184:23-185:1, and “[w]ith hindsight [he] believe[s] it would have been a good idea to read those patents,” *id.*, 186:14-15.

Dr. Falconer’s conceded legal errors undermine the weight afforded to his opinions. *BMW v. Stragent*, IPR2017-00676, 2018 WL 3005913, at *5 (P.T.A.B. June 14, 2018) (weight of opinion impacted where expert “did not provide responses

sufficient to conclude that he was aware of and/or applied the correct claim-construction standard”). The Board should not credit his Declaration’s written-description opinions, even had he defended them. But any possibility of Alvotech putting Humpty Dumpty back together again was extinguished when Dr. Falconer disavowed his ultimate opinion (*infra* §VII.B.2) and confirmed that, applying the correct legal standards and accounting for what was well known, the originally filed claims, and incorporated-by-reference materials, the POSA would recognize the inventors’ possession of the claims’ full scope (*infra* §VII.C-VII.C.2).

2. Dr. Falconer Agreed the Claims Are Adequately Described

Ground 3 advances two written-description arguments. As discussed *infra* §VII.C-VII.C.2, neither holds water. But Alvotech’s threshold problem is that it has only argument—not evidence—to support its challenge.

That is because both experts who opined on written description *agree* that the claims are adequately described. Dr. Falconer confirmed at deposition that “[t]here are numerous examples in the patent, both in the figures and in the written description portion describing formulations of aflibercept with at least 100 mgs per ml and viscosities of about 5 to 15 centipoise,” as recited by claim 1, Ex.2046, 179:8-13, as well as “extensive data on viscosities of particular high concentration aflibercept formulations,” *id.*, 167:19-23. Crucially, he acknowledged that “the description of those formulations provides adequate written description support for

claims claiming at least 100 mgs per ml of aflibercept with 5 to 15 centipoise viscosity.” *Id.*, 179:14-18. He thus conceded that he “do[es]n’t have an opinion that claim 31 lacks written description support,” *id.*, 193:18-21, and “do[es]n’t have an opinion that claim 35 lacks written description support,” *id.*, 194:4-7. Dr. Trout likewise agrees the claims are adequately described. Ex.2051, ¶¶238-331. Only Alvotech’s lawyers disagree, and their arguments cannot carry Alvotech’s burden. *Blackberry*, 2016 WL 1244943, at *14; *Intuitive*, 2020 WL 594140, at *16.

C. Alvotech’s Written-Description Theories Contradict the Specification’s Teachings and the POSA’s Knowledge

Even if the Board considers the merits based on Alvotech’s attorney argument, the Board should follow Dr. Falconer’s lead and reject them. Alvotech presses two arguments: first, that the specification discloses only “limited examples” insufficient to show the inventors’ possession of the claims’ “broad genus” of formulations, and second, that the claims do not recite “a buffer,” which “the specification makes clear is required.” Pet.75-86. Neither is availing.

1. Claims 31-38 Are Adequately Described

a. The Specification Discloses Representative Species and Common Structural Features

Claims 31 and 35 narrowly claim formulations comprising about 114.3 mg/ml and about 103-126 mg/ml aflibercept, respectively. Written description of these claims “requires the disclosure of either a representative number of species falling

within the scope of the genus or structural features common to the members of the genus so that [the POSA] can ‘visualize or recognize’ the members of the genus.” *Ariad*, 598 F.3d at 1350. There are no “bright-line rules governing ... the number of species that must be disclosed,” as it “changes with each invention” and “with progress in a field.” *Id.* at 1351. The central question is “whether the inventor ‘has truly invented the genus’ as opposed to ‘a research plan, leaving it to others to explore the unknown contours of the claimed genus,’” *Ajinomoto*, 932 F.3d at 1359.

Alvotech’s primary argument is that the claims cover a “broad genus of formulations” despite “disclos[ing] only a small number of species” that “are highly similar to one another...and do not reflect the full scope of the claims.” Pet.76-77, 80. But both experts disagree and testified that the specification discloses a representative number of species sufficient to demonstrate the inventors’ possession of the claims’ full scope. Alvotech cannot succeed.

As detailed *supra* §IV.A, and described by Dr. Trout, Ex.2051, ¶¶43-49, 240-261, the specification’s Examples 3, 5, and 9 disclose thirty-one exemplary formulations with concentrations of at least 100 mg/ml and viscosities of about 15 cP or less. Ex.1001, 9:46-11:26, 38:47-67, 42:17-22, Figs. 3B, 3C, 5, 9. These formulations have concentrations that either roughly encompass the claimed values (four 100 mg/ml and four 120 mg/ml formulations) or have higher concentrations (fourteen 140 mg/ml and nine 155 mg/ml formulations), which the POSA would

understand to show the inventors' possession of claims 31-38's lower-concentration formulations. *Id.*; Ex.2051, ¶¶274-280. The specification discloses an additional nine exemplary—and at least seven illustrative—formulations that would have the claimed viscosities at concentrations recited by claims 31-38—especially because all exemplary formulations with concentrations greater than 100 mg/ml but less than 140 mg/ml exhibit the claimed viscosities. Ex.1001, 9:41-10:29, 23:23-28:19, 38:32-40:11, 42:17-22, Figs. 3A, 3C, 5; Ex.2051, ¶¶277-280. The patent thus discloses at least forty-seven formulations the POSA would understand to support the inventors' possession of the claims. Ex.2051, ¶¶274-280.

These formulations are numerous and highly varied. They comprise over a dozen ingredients across wide concentration ranges, and reflect the inventors' possession of numerous techniques for achieving high-concentration, low-viscosity aflibercept formulations. These include adding six salts (sodium phosphate, sodium chloride, magnesium chloride, sodium sulfate, sodium thiocyanate, and sodium citrate); adding amino acids (glycine, lysine, histidine, arginine, sodium aspartate, and sodium glutamate); adjusting pH (decreasing from 6.0-5.8); and combinations thereof (sodium phosphate plus arginine). Ex.1001, 9:41-11:26, 23:23-28:19, 38:32-40:11, 42:17-22, 50:15-45, Figs. 3A-3C, 5, 9; Ex.2051, ¶¶248-253. This disclosure of nearly fifty distinct formulations employing multiple techniques—and a dozen different ingredients—to obtain the claimed viscosities refutes Alvotech's baseless

contention that the disclosed species are “highly similar” or “teach[] no more about making high-concentration formulations with the claimed viscosity levels than the prior art.” Pet.76, 80. As Dr. Falconer conceded, the “inventors provided extensive data on viscosities of particular high concentration aflibercept formulations in the patent” and “[t]here are numerous examples in the patent, both in the figures and in the written description portion describing formulations of aflibercept with at least 100 mgs per ml and viscosities of about 5 to 15 centipoise.” Ex.2046, 167:19-23, 179:8-13.

The POSA would predictably expect to achieve additional formulations within the claimed genus. Drs. Trout and Falconer agree that:

- The POSA would recognize the inventors’ use of salts, amino acids, and pH adjustment to obtain the claimed viscosities. Ex.2051, ¶¶249-253; Ex.2046, 88:24-89:4.
- All those strategies were well-known in the art. Ex.2051, ¶¶254-258, 307-314; Ex.1004, ¶¶52-66; Ex.2046, 88:2-6, 92:20-23, 93:25-94:4.
- The POSA, with the specification’s teachings, would understand that additional low-viscosity formulations could be achieved using those strategies. Ex.2051, ¶¶254-260; Ex.2046, 88:24-90:11.
- E.g., the POSA would recognize arginine and histidine as functioning analogously and would be “optimistic” that arginine could be used to

reduce viscosity given data (as in the specification) showing that histidine had done so. Ex.2046, 100:3-102:5; Ex.2051, ¶¶257-258, 313, 321, 324. Moreover, *every* exemplified formulation with a concentration inside the scope of claims 31-38 had a viscosity of less than 15 cP, and neither Dr. Falconer nor Alvotech identified any formulation—disclosed in the specification or otherwise—with a concentration of about 114.3 mg/ml or about 103-126 mg/ml that did not have that viscosity. Ex.2051, ¶¶274-280.

The specification’s forty-seven diverse formulations undisputably constitute representative species. Given these disclosures and well-known viscosity-reducing strategies, the POSA “could make predictable changes to the described [formulations]”—*e.g.*, by adjusting the pH or using different salts or amino acids or amounts thereof—“to arrive at other types of [formulations]” falling within claims 31-38. *Ajinomoto*, 932 F.3d at 1360-61. Likewise, the POSA would understand the forty-seven formulations to be “structurally similar to, and thus representative of,” the claimed genus more generally. *Id.* at 1360; *see* Ex.2051, ¶¶274-280. Dr. Falconer conceded representativeness, agreeing that “the description of those formulations provides adequate written description support for claims claiming at least 100 mgs per ml of aflibercept with 5 to 15 centipoise viscosity.” Ex.2046, 179:14-18; 57:20-58:1, 63:23-64:18, 63:4-12 (similar, for 103-126 mg/ml), 58:9-14 (114.3 mg/ml). Thus, *contra* Alvotech (Pet.80), the POSA clearly possessed

“sufficient information about which potential options for formulations will achieve the required viscosity levels and which will not,” such that the specification shows that “the inventor[s] ‘ha[ve] truly invented the genus’” of low-viscosity formulations, rather than disclosing a “research plan[] leaving it to others to explore the unknown contours of the claimed genus.” *Ajinomoto*, 932 F.3d at 1359.

Alvotech’s unsupported attorney arguments against representativeness are unavailing. Alvotech complains that “the viscosity data demonstrates that the specific formulation components and percentages matter to achieving the required viscosity levels,” but points only to histidine’s slightly superior performance to phosphate in reducing viscosity at higher aflibercept concentrations approaching 160 mg/ml. Pet.79. That complaint is meritless. *Infra* §VII.C.2.a. It is also inapplicable to claims 31-38, reciting concentrations (about 114.3 mg/ml or about 103-126 mg/ml) where histidine- and phosphate-containing formulations achieved near-identical viscosities. Ex.1001, 42:14-22, Fig.5; Ex.2051, ¶¶281-284. Neither Alvotech nor Dr. Falconer substantiated any notion that, within the concentration ranges of claims 31-38, the choice of ingredients (or amounts) determines whether the claimed viscosities are achieved; instead, all exemplary formulations with 100-120 mg/ml have viscosities around 10 cP or less. Ex.1001, 10:5-8, 10:24-29, 38:55-67, 42:17-22, Figs. 3C, 5; Ex.2051, ¶¶277-284. Similarly, Alvotech’s complaint that the species lack representativeness because “[t]here are *no examples* of [aflibercept]

concentrations above 155 mg/mL that achieve the required viscosity” is irrelevant to claims 31-38. Pet.79.

Alvotech’s cited authorities are inapposite. Pet.78-81. In *Pernix Ireland Pain DAC v. Alvogen Malta Operations*, 323 F. Supp. 3d 566 (D. Del. 2018), the specification provided a “detailed description” for only “a single operative embodiment,” providing no “guidance as to” which other formulations within the claimed genus “would satisfy the functional limitations of the claims.” *Id.* at 624-26. Here, in contrast, the specification discloses dozens of exemplary and illustrative formulations employing varying viscosity-reducing strategies, and the POSA knows how to employ different well-known strategies to achieve other low-viscosity formulations within the claimed genus. Ex.2051, ¶¶242-261, 274-280.

Alvotech’s reliance (Pet.78-80) on *AbbVie Deutschland GmbH v. Janssen Biotech*, 759 F.3d 1285 (Fed. Cir. 2014), also falls flat. The *AbbVie* claims recited an antibody genus defined by a “functional requirement” (k_{off} rate) “dependent on [antibody] structure,” but the specification disclosed only one “family of closely related, structurally similar antibodies”—“90% or more” similarity—and did not show possession of “antibodies having widely varying structures” differing by as much as “50%,” especially where only “80% sequence similarity” could have “completely different” binding. *Id.* at 1298, 1300. Here, the specification discloses numerous well-known strategies and structures (*e.g.*, salts, amino acids, pH

adjustment, and combinations thereof) for achieving the claimed viscosity. Unlike in *AbbVie*, the POSA here “could make predictable changes to the described [formulations] to arrive at other types of [formulations]” having the recited concentrations and viscosities. *Id.* at 1301; Ex.2051, ¶¶242-261, 274-280; Ex.2046, 100:3-102:5 (POSA “optimistic” about comparable viscosity reduction with arginine and histidine).

The POSA would recognize the patent to disclose common structural features demonstrating possession of the claimed genus, including non-exemplified formulations. The forty-seven exemplary and illustrative embodiments have the same structures: 100-155 mg/ml aflibercept, one or more amino acids and/or salts, and a pH of 5-6.8 (for exemplary formulations, 5.8-6.2). Ex.2051, ¶¶269-273, 285. Salts and amino acids were known structures sharing common structural features—combinations of positively and negatively charged ions (salts) or carbon, an amino group, a carboxyl group, and a side chain (amino acids). *Id.*; Ex.2046, 92:24-93:24, 94:5-97:3. The POSA could “‘visualize or recognize’ the members of the genus” recited by claims 31-38, such that the patent provides “a sufficient description of [the] genus.” *Ariad*, 598 F.3d at 1350; Ex.2051, ¶¶269-273, 285. Regeneron, Dr. Trout, and Dr. Falconer agree that the ’036 patent discloses dozens of high-concentration formulations as representative species—with common structural features—demonstrating the inventors’ possession of the claims 31-38 genus.

b. The Specification Discloses the Inventors’ Possession of Formulations Without a Buffer

Alvotech argues that the claims are invalid because they do not recite “a buffer” but the specification teaches one is necessary. Pet.83-86. Alvotech’s theory fails as a matter of law and fact.

i. Alvotech’s Arguments Misunderstand the Law

Alvotech profoundly misapprehends written-description law. To start, Alvotech’s insistence that claims that “do not recite a key limitation” lack written description—and its citation to *Gentry Gallery v. Berkline*, 134 F.3d 1473 (Fed. Cir. 1998)—is telling. Pet.85-86. The Federal Circuit assiduously rejected any notion that *Gentry* “announce[d] a new ‘essential element’ test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements.” *Cooper Cameron v. Kvaerner Oilfield Prods.*, 291 F.3d 1317, 1323 (Fed. Cir. 2002). Alvotech urges exactly what the Court foreclosed—an invalidity inquisition to divine which claim limitations are especially important. *See* Ex.2051, ¶¶289-290.

Alvotech also legally errs by demanding that the specification describe embodiments not recited by the claims. Section 112(a) requires only “an adequate written description of *what is claimed*.” *In re Entresto*, 125 F.4th 1090, 1099 (Fed. Cir. 2025) (emphasis added). Claims “encompass” various embodiments—*e.g.*, a claim reciting “a pharmaceutical composition comprising” two compounds “in

combination” would encompass “complexes” of the two compounds. *Id.* at 1095, 1097. But written description assesses “whether the [challenged] patent describes what is claimed, ... not whether [it] ... describes [a particular embodiment of] complexes. Because the [challenged] patent does not claim ... complexes, those complexes need not have been described.” *Id.* at 1097. The same holds here. *Contra* Alvotech (Pet.83), the ’036 patent does not claim “formulation[s] that achieve[] the claimed viscosity levels without a buffer”; rather, claims 31-38 recite formulations “comprising” high-concentration aflibercept that may or may not include a buffer. Ex.2046, 169:14-17. Because the patent covers, but does not claim, formulations “without a buffer,” (Pet.83) such formulations “need not have been described.” *Entresto*, 125 F.4th at 1097. The claims would not lack written description even were Alvotech correct (it is not, *infra* §VII.C.1.b.ii) that the specification fails to convey possession of formulations without a buffer. Ex.2051, ¶¶287-288.

Alvotech errs again by suggesting that the specification must disclose specific, excipient-buffer-free embodiments. Pet.83. “There is no rigid requirement that the disclosure contain ‘either examples or an actual reduction to practice,’” *Allergan*, 796 F.3d at 1308, nor need it “describe in the specification every conceivable and possible future embodiment of [the] invention,” *Cordis v. Medtronic*, 339 F.3d 1352, 1365 (Fed. Cir. 2003). Alvotech’s challenge fails.

**ii. The Disclosure Teaches That Buffers Are
“Optional” and That the Inventors Possessed
Formulations Without Buffers**

Alvotech’s challenge also lacks factual support. Alvotech cites nothing in the specification characterizing buffers as “necessary.” It argues that buffers, unlike other ingredients, are never *expressly* labeled “optional”—thereby implicitly conceding that the specification nowhere labels buffers “mandatory.” Pet.83-84; Ex.1004, ¶284. The POSA considering not only that specification disclosure but also the original disclosure, incorporated-by-reference materials, and information well-known in the art—each of which teaches the optionality of buffers—would understand buffers to be optional. Ex.2051, ¶¶289-331.

Original Disclosure. The originally-filed claims recite formulations without a buffer, dooming Alvotech’s argument. In both the application that issued as the ’036 patent and the application that issued as U.S. Patent 11,103,552—to which the ’036 patent claims priority—original claim 30 recited treatment methods “comprising administering an intraocular injection of more than about 2 mg of a VEGF receptor fusion protein,” while claim 31 recited higher doses, including “about 8 mg.” Ex.2054, 66-67; Ex.1002, 4931-32; Ex.2051, ¶¶294-297. Only dependent claim 37 recited a “buffer” (“histidine buffer”), confirming that these original claims do not require one. *Id.*

Because “[o]riginally filed claims” are “part of the specification” and must “be considered in any § 112 analysis,” original claims 30-36 in both “application[s] disclosed formulations without a [buffer].” *Allergan*, 111 F.4th at 1374. Given that inventors demonstrate possession of an embodiment by “disclos[ing] it in an original claim,” that Regeneron “successfully obtained a patent including the originally filed claim”—amended to recite additional limitations but, crucially, not a buffer—means that the patent’s “claim[s], which do[] not require ... a [buffer], would ***undoubtedly have satisfied the written description requirement of § 112 ... because it would be directly supported in haec verba by the disclosure.***” *Id.*

Drs. Falconer and Trout concur that these claims satisfy written description. Dr. Falconer agreed that “[i]f the originally filed claims for the application that issued as the ’036 patent included claims” to “administering an intravitreal injection of a VEGF receptor fusion protein without requiring a buffer,” that “would...provide written description support in [his] opinion.” Ex.2046, 171:18-172:2. He conceded that original “claims 30 through 36” meet that precise description and “don’t require a buffer.” Ex.2046, 173:24-175:21; *see* Ex.2051, ¶¶294-297. The experts agree—and the law is clear—that the original claims dispose of Alvotech’s buffer-based challenge.

Incorporation. Were additional proof needed, materials the specification incorporates by reference confirm the optionality of buffers. The specification

states: “multimerization component (‘FcΔC1(a)’) comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, i.e., K458, may or may not be included in the VEGF receptor fusion proteins, *see U.S. Pat. No. 7,396,664 or 7,354,579, incorporated herein for all purposes*).” Ex.1001, 16:10-15 (emphasis added). The POSA would understand this language to incorporate the entirety of those two patents “with sufficient particularity,” *Harari*, 656 F.3d at 1334; *Paice*, 881 F.3d at 907, as Dr. Trout explained, Ex.2051, ¶¶291-293, and Dr. Falconer agreed, Ex.2046, 185:22-25 (“Q. And you understand that the ’036 patent incorporates those patents herein for all purposes, right? A. That’s what the sentence says, yes.”).

Those incorporated-by-reference patents—which are effectively part of the specification, *Arbutus*, 65 F.4th at 662-63—teach the optionality of buffers by instructing that “[t]he composition, *if desired, can also contain* minor amounts of wetting or emulsifying agents, or *pH buffering agents*.” Ex.2047, 12:30-32; Ex.2048, 5:13-15 (emphases added). This incorporated disclosure that buffers can “also” be included “if desired” reinforces that the POSA reading the specification would understand the inventors to possess buffer-optional formulations. *Id.*; Ex.2051, ¶¶291-293. Dr. Falconer conceded that (1) “[i]f the specification of the ’036 patent incorporated language indicating that the use of a buffering agent was optional, then [he] would agree that [his] written description opinion would [not]

apply”; (2) “[his] interpretation of that sentence” in the incorporated-by-reference patents “would be” “that a buffer is used only if desired”; and (3) “if that language...were incorporated into the ’036 patent then [he] agree[s] that the ’036 patent would include language indicating that the use of a buffer is optional.” Ex.2046, 176:23-178:18. His declaration never considered those incorporated patents. Ex.2046, 184:23-185:1, 186:14-15. *Contra* Alvotech (Pet.83-86), the specification, including the original claims and incorporated-by-reference patents, conclusively establishes possession of buffer-optional formulations.

Well-Known Viscosity-Reduction Strategies. For two additional reasons, the specification conveys the inventors’ possession of formulations without a buffer. As before, adding salts, adding amino acids, and adjusting pH were well-known viscosity-reduction strategies, Ex.2051, ¶¶254-258, 307-315; Ex.1004, ¶¶52-66; Ex.2046, 88:2-6, 92:20-23, 93:25-94:4, and the POSA understood the inventors disclosed those strategies (and combinations thereof) to achieve the claimed viscosities with high-concentration aflibercept, Ex.2051, ¶¶248-260; Ex.2046, 88:24-90:11. The POSA also understood that while some disclosed viscosity-reducing amino acids and salts functioned as buffers in the exemplary formulations within their 5.8-6.2 pH range (*e.g.*, histidine and sodium citrate), other viscosity-reducing amino acids and salts had only attenuated buffering capacity within that pH range (*e.g.*, sodium phosphate) or no buffering capacity because they either lacked

buffering structure (*e.g.*, magnesium chloride) or had pK_a 's too far from that pH range (*e.g.*, arginine). Ex.1001, 2:61-3:8, 10:5-8, 10:45-11:26, 38:32-40:11, 42:14-22, 46:34-51:13, Figs. 3A-3C, 5, 9; Ex.2057, 575; Ex.2056, 1126; Ex.2051, ¶¶306-324; Ex.2046, 86:17-88:23, 93:16-24, 95:14-17, 165:20-24, 167:5-18. As Dr. Falconer agreed, the patent teaches “the strategies of adding amino acids and adding salts” to reduce viscosity, and those strategies “encompass adding buffers” like histidine and adding ingredients like arginine, lysine, and sodium chloride that are not buffers at the relevant pH. Ex.2046, 92:13-95:17, 100:12-18, 167:1-18. The POSA would recognize that whether a given amino acid or salt reduces viscosity does not depend on whether it happens to function as a buffer, but instead whether it disrupts protein-protein interactions (which drive increased viscosity). Ex.2051, ¶¶306-324; Ex.1028, 539, 542; Ex.1021, 193-94, 199-206; Ex.1044, 4478, 4481.

Accordingly, the specification teaches the POSA to use amino acids and/or salts to achieve the claimed low-viscosity formulations, regardless of whether the substances are buffering. Ex.2051, ¶¶306-324. The exemplary formulations' inclusion of a buffer reflects that a salt or amino acid reduces viscosity—not that significant buffering capacity is required to achieve the claimed viscosities. *Id.* Dr. Falconer agreed: “if you had data showing that histidine reduced viscosity for a particular protein at a particular concentration”—as the patent discloses, Ex.1001, 38:47-40:11, 42:14-22, Figs.3B, 5—then “the POSA would be optimistic that

arginine”—also an amino acid, but not a buffer—“could also serve to reduce the viscosity of that protein at that concentration.” Ex.2046, 100:12-18; Ex.2051, ¶¶257-258, 313, 321, 324. The specification thus conveys that buffer and non-buffer salts, and buffer and non-buffer amino acids, all can achieve the claimed low-viscosity formulations, notwithstanding the examples’ inclusion of buffer salts or buffer amino acids. Ex.2051, ¶¶306-324. The POSA understood buffers are optional and would recognize the inventors’ possession of formulations without them. *Id.* Alvotech’s legally improper requirement that the specification disclose non-buffered formulations, *Allergan*, 111 F.4th at 1374-75, is thus satisfied.

Second, the specification discloses that “buffers” are “viscosity reducing agents” and thus optional. The patent repeatedly teaches that “buffers”—including histidine, phosphate, and citrate—are used to reduce viscosity. Ex.1001, 2:65-66, 38:52-54, 42:14-22, 46:29-50:67, Figs. 5, 9; Ex.2051, ¶¶306-316, 325-328; Ex.2050, ¶¶31, 45, 49 (phosphate as “viscosity reducing agent” and “buffer”); Ex.2005, 3234 (histidine, phosphate, and citrate buffers as viscosity reducers). The specification employs the “well known” viscosity-reducing “strategies of adding amino acids and adding salts,” which “encompass adding buffers.” Ex.2046, 86:17-88:23, 165:20-24, 167:1-9. The specification explicitly and repeatedly characterizes viscosity-reducing agents as “optional.” Ex.1001, 2:36-38, 2:48-49, 3:21-23, 5:60-63, 15:2-3, 20:2-4, 20:31-41, 23:46-25:61, 28:54-58; Ex.2051, ¶¶306-316, 325-327; Ex.1004,

¶¶279-83. Given the repeated instruction that buffers are used to reduce viscosity, and that viscosity reducers are optional, the POSA would understand that “buffers,” like viscosity reducers generally, are optional in the claims. Ex.2051, ¶¶306-316, 325-327.

The POSA thus would recognize the inventors’ possession of formulations that do not include a “buffer.”

Alvotech’s reliance (Pet.85) on *LizardTech v. Earth Resource Mapping*, 424 F.3d 1336 (Fed. Cir. 2005), is unavailing. There, a claim that “refer[red] to taking a seamless DWT generically” lacked written description because “[t]he specification provide[d] only a single way of creating a seamless DWT” and never “contemplate[d] a more generic way” of doing so. *Id.* at 1344. But here, as Dr. Trout explains and Dr. Falconer testified, the specification discloses numerous well-known strategies for obtaining the claimed low-viscosity formulations, including adding amino acids or salts, regardless of whether they are buffering. Ex.2051, ¶¶248-261, 306-324; Ex.2046, 167:1-18.

Finally, viscosity aside, the POSA understood that buffers were not generally necessary in high-concentration aflibercept formulations. Protein formulations lacking an excipient buffer were known, and the POSA understood that fusion proteins like aflibercept have buffering capacity, especially at higher concentrations. Ex.2051, ¶¶299-305; Ex.2039, 3; Ex.2046, 208:23-212:4; Ex.2021, 3:15-4:8, 3:49-

4:5, 38:21-32, 41:6-16, 43:12-19, 44:31-34, 45:1-18, 78:1-80:14, Figs. 10-11, 14-16; Ex.2049, 757. Dr. Falconer agreed that “starting in the 2000s the POSA was familiar with the concept of a therapeutic monoclonal antibody formulation in liquid form that did not require an excipient buffer,” that “the POSA would understand that aflibercept could be formulated without an excipient buffer,” and that, “in view of the disclosure of the ’036 patent the POSA would understand that a formulation with at least 100 mgs per ml of aflibercept could be formulated without an excipient buffer.” Ex.2046, 212:8-12, 214:12-21. The POSA reading the patent thus would understand that buffers were not required in the claimed high-concentration aflibercept formulations. Ex.2051, ¶¶299-305. And because a “patent need not teach, and preferably omits, what is well known in the art,” *McRO*, 959 F.3d at 1102, the specification need not expressly state that aflibercept can be formulated without a buffer.

2. Claims 1-30 Are Adequately Described

Alvotech’s written-description challenge to claims 1-30 fails for the same reasons as claims 31-38. First, the specification discloses representative species and common structural features for the claim 1 genus. Second, the claims are not invalid because they do not recite a buffer.

a. The Specification Discloses Representative Species and Common Structural Features

For largely the same reasons as for claims 31-38, the POSA understood the specification to disclose representative species demonstrating the inventors' possession of the claim 1 genus of formulations. *Supra* §VII.C.1.a. The specification discloses thirty-one exemplary formulations with concentrations greater than 100 mg/ml and viscosities less than 15 cP, employing numerous well-known viscosity-reducing strategies (*e.g.*, adding salts, adding amino acids, adjusting pH, and combinations thereof) and comprising many distinct ingredients, including six salts and six amino acids. Ex.2051, ¶¶242-261. The POSA predictably would adjust the disclosed formulations (*e.g.*, employing different salts or amino acids or amounts thereof) to make additional claimed formulations—especially since salts and amino acids are well-known substances with common structural features—and would recognize the disclosed formulations as representative of the claimed genus. *Id.* As Dr. Falconer admitted, “the description of those formulations provides adequate written description support for claims claiming at least 100 mgs per ml of aflibercept with 5 to 15 centipoise viscosity.” Ex.2046, 167:19-23, 179:8-18. The patent indisputably discloses representative species for claim 1. Ex.2051, ¶¶242-261.

None of Alvotech's arguments specific to claim 1 (and inapplicable to claims 31-38)—*i.e.*, the purported lack of formulations with a concentration above 160

mg/ml but a viscosity less than 15 cP, or histidine’s superior viscosity-reducing performance at higher concentrations, Pet.79—support a contrary finding. To start, the POSA would recognize claim 1’s “workable” upper limit around 160 mg/ml and the specification adequately describes formulations with concentrations approaching that limit. *Regeneron*, 127 F.4th at 916 (““open-ended claims” adequately described “where the upper bound ‘would be limited by what a [POSA] would understand to be workable’ and where the patent’s specification adequately supported that range”). The exponential nature of concentration-viscosity curves was well-known. Ex.2051, ¶¶90-92, 128-129, 262-264; Ex.1021, 194; Ex.1027, 748; Ex.2005, 3233; Ex.2046, 106:8-10. Absent experimental data, the POSA would not know the shape of aflibercept’s exponential curve, including the “threshold” concentration above which viscosity steeply increases, such that low-viscosity formulations cannot be attained. *Supra* §VI.B.1.b.i.1; Ex.2051, ¶¶95-96, 129, 221, 263; Ex.1027, 748. The parties agree that the patent’s experimental data convey a threshold for aflibercept of around 160 mg/ml, where the concentration-viscosity curve very steeply increases, and above which no formulations with a viscosity below 15 cP are reported:

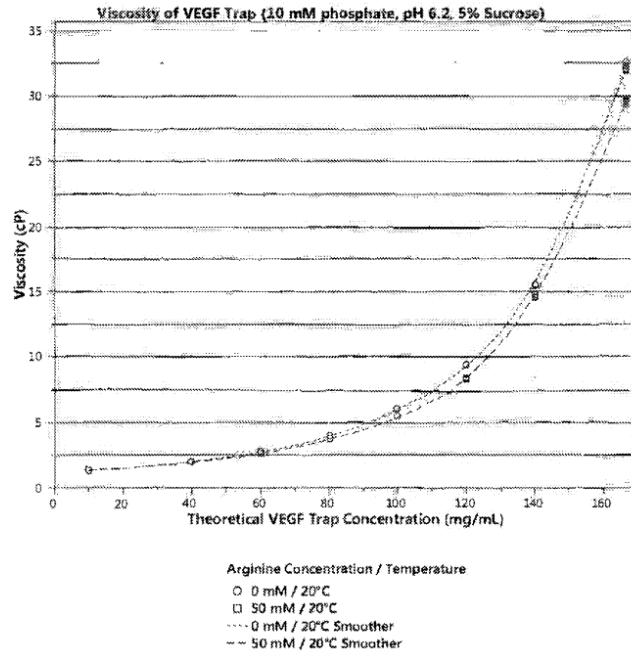


FIG. 3C

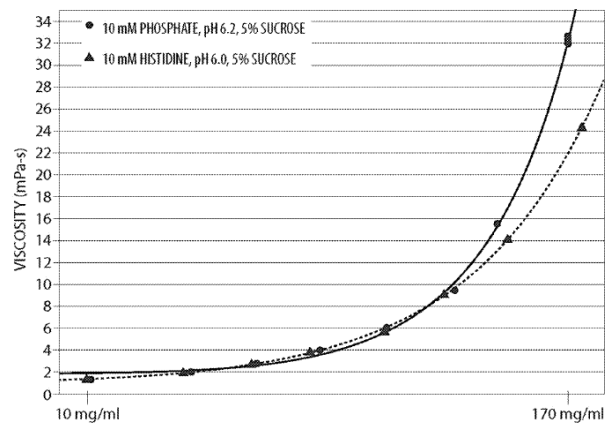


FIG. 5

Ex.1001, Figs. 3C, 5; Ex.2051, ¶¶262-268; Ex.1004, ¶274 (“Figure 5 demonstrates that, above about 160 mg/mL, the viscosity of both phosphate and histidine-containing formulations falls well above the claimed range[.]”); Pet.71 (“[A] skilled formulator would have determined the range of possible concentrations for aflibercept in the aqueous pharmaceutical formulation is 80[-]160 mg/mL.”). The

POSA thus recognized a workable upper limit for the claimed formulations around 160 mg/ml, and would understand the specification supported that whole range by disclosing thirty-one representative species comprising concentrations from 100-155 mg/ml (92% of the range), including nine 155 mg/ml formulations with viscosities ranging from 11.4 cP to 14.1 cP. *Supra* §VII.C.1.a; Ex.2051, ¶¶262-268; Ex.2046, 161:9-19, 163:2-165:19 (Dr. Falconer did not “specifically” “recall” undertaking the analysis required for open-ended claims).

That certain phosphate-containing formulations comprising 140 or 155 mg/ml aflibercept have viscosities higher than histidine-containing formulations and above the claimed range does not endorse a contrary finding. The POSA would recognize, as depicted in Figure 5, that histidine- and phosphate-containing formulations perform comparably across most of the 100-160 mg/ml range, with separation observed only at the upper extremity. Ex.2051, ¶¶262-268; Ex.1001, 38:32-40:11, 42:19-21, Figs. 3A-3C, 5. Histidine’s slightly superior performance is not surprising, as amino acid salts interact both electrostatically and hydrophobically. Ex.2051, ¶¶262-268, 307-308; Ex.1021, 194, 199-201, 203, 205-06. Given Example 3’s instruction that every additional salt and amino acid used in the phosphate-containing 155 mg/ml formulations resulted in decreased viscosity—with greater concentrations causing greater reductions—the POSA recognized the inventors’ possession of phosphate-containing formulations at 140-160 mg/ml using higher

amounts of other amino acids or salts to reduce viscosity to within the claimed range. Ex.2051, ¶¶262-268; Ex.1001, 38:32-40:11, Figs. 3A, 3C. The POSA would overcome any difference in viscosity reduction between histidine and phosphate at concentrations approaching the workable upper limit by using higher concentrations of other salts and amino acids that the specification discloses reduce the viscosity of phosphate-containing formulations. Ex.2051, ¶¶262-268. The specification discloses representative species for claims 1-30.

Additionally, for the same reasons as claims 31-38, the patent discloses common structural features for claims 1-30, *i.e.*, 100-155 mg/ml of a VEGF receptor fusion protein at a pH of 5.8-6.2, and with one or more salts and/or amino acids. *Supra* §VII.C.1.a; Ex.2051, ¶¶269-273.

b. The Specification Discloses the Inventors' Possession of Formulations Without a Buffer

For the reasons explained *supra* §VII.C.1.b, the specification demonstrates the inventors' possession of formulations of claims 1-30 that do not include a "buffer."

VIII. Conclusion

Regeneron respectfully requests that the Board confirm the patentability of the challenged claims.

Date: June 19, 2026

/David I. Berl/
David I. Berl

Reg. No. 72,751
Williams & Connolly LLP
680 Maine Avenue SW
Washington, D.C. 20024
Lead Counsel for Patent Owner

CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

In accordance with 37 C.F.R. § 42.24, as amended, the undersigned certifies that this Patent Owner Response complies with the applicable type volume limitations of 37 C.F.R. §§ 42.24(a)(ii) and 42.24(b)(1). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Patent Owner Response contains 18,654 words as counted by the word processing program used for its preparation (Microsoft Word).

Date: June 19, 2026

/David I. Berl/

David I. Berl

Reg. No. 72,751

Lead Counsel for Patent Owner

CERTIFICATE OF SERVICE
(37 C.F.R. § 42.6(e))

The undersigned hereby certifies that on June 19, 2026, I caused true and correct copies of the following materials:

- Patent Owner's Response
- Patent Owner's Updated List of Exhibits
- Patent Owner's Motion to Seal
- Exhibits 2037-2092, 2094-2113, 2115-2118, and 2120-2143

to be served via e-mail on the following:

Name	E-Mail Address
Martina Hufnal	PGR46514-0017PS1@fr.com
Michael Kane	PGR46514-0017PS1@fr.com
Kristi L. R. Sawert	PGR46514-0017PS1@fr.com
Nitika Fiorella	PGR46514-0017PS1@fr.com
Megan A. Chacon	PGR46514-0017PS1@fr.com
Deanna Reichel	PGR46514-0017PS1@fr.com
Phillip Chen	PGR46514-0017PS1@fr.com

Date: June 19, 2026

/David I. Berl/
David I. Berl
Reg. No. 72,751
Lead Counsel for Patent Owner